

Time trends of childhood food allergy in China: three cross-sectional surveys in 1999, 2009, and 2019

Zhuoying Ma¹⁻³, Lin Chen²⁻³, Ruoling Xian²⁻³, Heping Fang²⁻³, Juan Wang¹⁻³, Yan Hu¹⁻⁴

Author's institutional affiliations: 1.Department of Child Health Care, Children's Hospital of Chongqing Medical University, Chongqing, P.R. China. 2.Ministry of Education Key Laboratory of Child Development and Disorders, National Clinical Research Center for Child Health and Disorders (Chongqing), China. 3.International Science and Technology Cooperation base of Child development and Critical Disorders. 4.Chongqing Key Laboratory of Child Health and Nutrition.

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Corresponding author's name: Yan Hu. **Affiliation:** Department of Child Health Care, Children's Hospital of Chongqing Medical University, Chongqing, P.R. China. **Address :** No.136, 2nd Zhongshan Road, Yuzhong District, Chongqing, 400014, China. **E-mail :** hy420@126.com. Telephone number: +86 13896015172

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DR ZHUO-YING MA (Orcid ID : 0000-0001-6694-7721)

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Zhuoying Ma¹⁻³, Lin Chen²⁻³, Ruoling Xian²⁻³, Heping Fang²⁻³, Juan Wang¹⁻³, Yan Hu¹⁻⁴

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Abbreviations

FA: Food allergy

SPT: Skin prick test

OFC: Open food challenge

CMPA: Cow's milk protein allergy

CI: Confidence interval

Abstract

Background: Many countries have recorded the trends of food allergy (FA) prevalence.

Little is known about epidemiological trends of childhood FA in China.

Methods: In three cross-sectional surveys conducted in 1999, 2009, and 2019, the prevalence of and characteristic changes in FA in children aged ≤ 2 years were assessed and the outcomes were compared. All the children were recruited during well-baby check-ups at the Children's Hospital of Chongqing Medical University. All participants had a detailed medical history taken and underwent skin prick tests using ten commercial food extracts. Open food challenges were used for confirmation of FA.

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Results: The three studies included 1228 children (314 in 1999; 401 in 2009; and 513 in 2019; response rate > 95 %). The prevalence of FA in 2009 (7.7%) and 2019 (11.1%) was significantly higher than that in 1999 (3.5%). However, there was no statistically significant difference in prevalence between 2009 and 2019 ($P = 0.086$). There was evidence of increased prevalence in CMPA between 1999 and 2019 (1.6% versus 5.7%; $P=0.004$); However, no statistic difference was found in egg allergy (2.9% versus 5.5%; $P=0.21$). The incidence of skin symptoms did not differ significantly over the study period, while the incidence of gastrointestinal symptoms increased significantly (18.2% in 1999, 12.9% in 2009, and 43.9% in 2019; $P<0.05$).

Conclusions: The prevalence of FA in children rapidly increased after the 1990s and gradually stabilized after 2010. Cow's milk has become the most common food allergen among children in Chongqing. The incidence of gastrointestinal symptoms as a manifestation of FA has increased significantly since 2010.

Key Message: Data from three cross-sectional surveys conducted in 1999, 2009, and 2019 showed that the prevalence of food allergy in children increased after the 1990s and gradually stabilized after 2010. Cow's milk has become the most common food allergen among children in Chongqing. The incidence of gastrointestinal symptoms as a manifestation of food allergy has increased significantly since 2010. The findings may help clinicians understand the epidemiological trends of food allergy in Chinese children over the past 20 years.

Key words: Cross-sectional study; Food allergy; Children; Prevalence; Time trends;

Introduction

FA is one of the most common childhood allergic diseases, affecting 5% (1–10%) of children aged 0–5 years worldwide.¹ Since the beginning of the 21st century, most studies have shown that the prevalence of FA is on the rise. The yearly hospitalization rates of patients with food-induced anaphylaxis in developed countries such as the United States,² United Kingdom,³ and New Zealand⁴ have also increased since 2010. Therefore, FA has been described as the “second wave” of allergic diseases after asthma and allergic rhinitis.⁵

However, recent data suggest that the prevalence of FA is stabilizing or beginning to decline. In an analysis of two Melbourne cohorts, Peter et al.⁶ reported that the prevalence of food sensitization among high-risk infants with an atopic family history has remained stable since the 1990s. In the United Kingdom,⁷ the prevalences of peanut sensitization at the age of

1 year in two birth cohorts recruited 12 years apart (1989 and 2001–2002) were nearly identical. The prevalence of peanut allergy at the age of 10 years was higher in the 2001–2002 cohort (1.5% versus 0.58%); however, this difference was not statistically significant ($P=0.09$). A Canadian study also indicated that there was no difference in the prevalence of physician-confirmed child (<18 years) allergies between 2010 and 2016 (5.9% versus 6.1%).⁸ Willits et al. found that the incidence of FA increased markedly between 2002 and 2009, and has stabilized in the United States since 2009.⁹ In Spain, a comparison of two multi-center cross-sectional studies conducted in 2005¹⁰ and 2015¹¹ found that although there was no difference in the type of food causing allergic reactions, the incidence of FA diagnosed by specialists among children aged <5 years decreased (68.3% and 19.5%, respectively).

The above conclusions about FA over time were derived from the comparison of data from cross-sectional surveys or birth cohorts. However, these conclusions were influenced by the purpose, methodology, sample frame, and outcome measures of the original studies. Therefore, repeated cross-sectional studies in the same region using the same methodology to confirm FA are needed to understand the epidemiological trends. In 1999, 2009, and 2019, we conducted three cross-sectional studies on the prevalence of FA in Chongqing, China, using the same survey methods. Our previous article reported that the prevalence of FA in 0-2-year-old children increased from 3.5% in 1999 to 7.7% in 2009 ($P=0.017$)¹². The current study is unique because we included the 2019 cohort to describe the regional epidemiological trends of FA in Chinese children over the past 20 years.

Methods

Data from three cross-sectional surveys with the same diagnostic methods involving the same patient age group (0–24 months) performed at the same clinic were assessed. Children were enrolled during well-baby check-ups at the division of Child Health Care of Children's Hospital of Chongqing Medical University, which is the only children's hospital in the main districts of Chongqing. Medical histories were obtained, and the skin prick test (SPT) was performed in all eligible participants. SPT was considered positive when the mean wheal diameter was at least 3 mm greater than the negative control at 15 minutes. Food elimination tests were carried out for those with positive results of SPT and all patients with suspected non-IgE mediated allergy who improved significantly after elimination for 2 weeks (Figure 1). Children whose symptoms improved significantly with the elimination of the implicated allergen were further evaluated by OFC. OFC was performed in the hospital by a trained pediatrician, and the subjects were observed for at least 2 hours after the last dose before

going home. Parents were asked to report any symptoms that occurred in the 3 days following after OFC. If any reactions suspicious of FA were reported, the children were to be brought to the hospital for appropriate management immediately. OFC results were used as diagnostic criterion for FA¹³ in accordance with the EAACI Guidelines¹⁴, which has depicted in more detail in a previous article¹². Any participant with an incomplete diagnostic process was considered a drop-out. The antigen extracts used in the SPT included those obtained from egg yolk, egg white, cow's milk, soybean, peanut, wheat, fish, shrimp, orange, and carrot (purchased from Greer Company, USA).

The 1999 survey was conducted between May 1999 and June 1999 (N=314).

The 2009 survey was conducted between June 2009 and July 2009 (N=401).

The 2019 survey was conducted between June 2019 and August 2019 (N=513).

This study was approved by the ethics committee of the Children's Hospital of the Chongqing Medical University, China (clinical trial registration number: ChiCTR1900024338). The children's guardians/parents provided informed consent, and the studies were carried out in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

All data were double entered by different operators on Microsoft Excel, and SPSS 23.0 (SPSS Inc, Chicago, IL, USA) was used for data analysis. Quantitative data were expressed as the number of cases (%). The 95% confidence intervals (CI) for FA prevalence were calculated assuming a Poisson error distribution. The χ^2 test was used in when the linear and quadratic components of a trend were isolated; pairwise comparisons and cochrane-armitage trend tests were used. $P < .05$ was considered statistically significant.

Results

Survey characteristics

In the 1999 survey, a total of 314 patients were eligible but 10 of them dropped out during the food elimination tests. Therefore, 304 children were included in the analysis (response rate 96.8%). In the 2009 survey, a total of 401 children were eligible and 19 dropped out, thus the overall response rate were 95.3% (382/401).

A total of 513 children (268 boys and 245 girls) were eligible for the 2019. Among them, 379 were 0-12 months old, and 84 were 12-24 months old. During the diagnostic period, 10 children dropped out, and 503 children completed the survey. The response rate was 98.1% (503/513). There were no differences in sex and age distributions and in the response rates among the participants in the three surveys ($P > .05$).

Prevalence of parent-reported FA

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The prevalence of FA reported by parents in the three surveys was 13.7% (43/314, 95% CI 9.9-17.5%), 16.7% (67/401, 95% CI 13-20.4%), and 22.8% (117/513, 95% CI 19.2-26.5%) in 1999, 2009, and 2019, respectively; the differences were statistically significant ($\chi^2=11.982$, $P=0.003$) (Table I). After a pairwise comparison, there was no significant difference in the prevalence of parent-reported FA in 2009 and 1999 ($\chi^2=1.229$, $P=0.268$). Meanwhile, in 2019, it was significantly higher than in 1999 ($\chi^2=10.366$, $P=0.001$) and 2009 ($\chi^2=5.207$, $P=0.023$) (Figure 2-A).

Prevalence of food sensitization

Comparing the three studies, the rate of SPT-positivity to any of tested food changed significantly in 20 years ($\chi^2=9.405$, $P=0.009$), with the highest positive rate in 2009 (72/401, 18.0%, 95% CI 14.2-21.7%), followed by 2019 (80/513, 15.6%, 95% CI 12.4-18.7%), and 1999 (31/314, 9.9%, 95% CI 6.6-13.2%). The positive SPT result rate in 1999 was lower than that in 2009 ($\chi^2=9.330$, $P=0.002$) and 2019 ($\chi^2=5.488$, $P=0.019$). There was no significant difference between 2009 and 2019 ($\chi^2=0.905$, $P=0.342$) (Table I, Figure 2-B).

In all the three studies, the most common foods causing sensitization were egg and milk. The prevalence of the various sensitizations were described in table 2. The temporal variation trend of egg and milk sensitization was consistent with the general trend of food sensitization. The prevalence of egg sensitization increased from 7.3% in 1999 to 15.5% in 2009 ($\chi^2=11.130$, $P=0.001$), and decreased afterward to 11.5%, although the decline was not statistically significant ($\chi^2=3.073$, $P=0.08$).

Prevalence of FA

According to the diagnostic process, there were 21 cases (21 with positive SPT) of suspected FA that underwent OFC in 1999, 45 cases in 2009 (26 with positive SPT and 19 with positive history), and 88 in 2019 (66 with positive SPT and 22 with positive history). The prevalence of FA confirmed by OFC varied from 3.5% (11/314, 95% CI 1.5-5.6%) in 1999 to 7.7% (31/401, 95% CI 5.1-10.4%) in 2009 to 11.1% (57/513, 95% CI 8.4-13.8%) in 2019 ($\chi^2=14.803$, $P=0.001$) (Table I). However, a pairwise analysis showed that although the prevalence of FA in 2009 and 2019 were higher than that in 1999 ($\chi^2=5.692$, $P=0.017$ and $\chi^2=14.939$, $P<0.001$), there was not a statistically significant difference in prevalence between 2009 and 2019 ($\chi^2=2.956$, $P=0.086$) (Figure 2-C).

Among the 19 children with negative SPT but with a history of parent-reported adverse reaction to foods in 2009, 2 children (2/401, 0.5%) were diagnosed with non-IgE mediated FA by OFC. While in the 2019 survey, 18 of 22 participants (18/513, 3.5%) were diagnosed

with non-IgE-mediated FA. The prevalence of non-IgE-mediated FA increased significantly ($\chi^2=9.527$, $p=0.002$). No similar cases were found in the 1999 survey.

IgE-mediated allergies prevalence were 3.5% in 1999, 7.2% in 2009, and 7.6% in 2019 respectively. After a pairwise comparison, there was no significant difference in the prevalence of IgE-mediated FA in 2009 and 2019 ($\chi^2=0.045$, $P=0.832$). Meanwhile, in 1999, it was significantly lower than in 2009 ($\chi^2=4.636$, $P=0.031$) and 2019 ($\chi^2=5.762$, $P=0.016$).

The most common FA was egg allergy, with a prevalence of 2.9% (9/314, 95% CI 1-4.7%), 5% (20/401, 95% CI 2.9-7.1%), and 5.5% (28/513, 95% CI 3.5-7.4%) in 1999, 2009, and 2019, respectively. However, the prevalence of egg allergy over time was not statistically significant ($\chi^2=3.117$, $P=0.210$). The prevalence of CMPA was 1.6% (5/314, 95% CI 0.2-3%), 3.5% (14/401, 95% CI 1.7-5.3%), and 5.7% (29/513, 95% CI 3.7-7.7%) in 1999, 2009, and 2019 respectively. Although there was no significant difference in CMPA between 1999 and 2009 ($\chi^2=2.346$, $P=0.126$), and 2009 and 2019 ($\chi^2=2.455$, $P=0.117$), the prevalence of CMPA increased significantly over a 20-year period (1999-2019, $\chi^2=8.147$, $P=0.004$) (Figure 3).

Challenge-confirmed manifestations of FA

Over the past 20 years, the most common clinical manifestations in children with FA were skin symptoms (with an average incidence of 78.6%) such as eczema and urticaria, followed by gastrointestinal symptoms, characterized by oral allergy syndrome, vomiting, bloody stools, and diarrhea. The average incidence of gastrointestinal symptoms was 25.0% (Table III). Respiratory symptoms in patients with FA were uncommon and were always accompanied by gastrointestinal or cutaneous symptoms.

In the three studies, skin symptoms were the most common symptoms ($\chi^2=5.004$, $P=0.082$). However, while the incidence of gastrointestinal symptoms in FA remained stable between 1999 and 2009 ($\chi^2=0.275$, $P=0.7$), it increased from 12.9% to 43.9% between 2009 and 2019 ($\chi^2=11.068$, $P=0.001$), most of them were induced by cow's milk (14/25, 56%) (Table III).

Life-threatening food-induced anaphylaxis was rare in all three surveys. Only a 7-month-old boy in the 2019 survey presented with severe periorbital edema, systemic urticaria, cough, and listlessness 1.5 hours after the egg OFC.

Discussion

Comparison of data from cross-sectional epidemiological surveys conducted at different points in time is a good method to obtain the trend of FA prevalence over time. However, the conclusions are influenced by the original purpose of the study, design of the protocol,

characteristics of the sample, and diagnostic criteria. We conducted three surveys over a 20-year period and showed that both the prevalence of food sensitization and confirmed FA increased significantly between 1999 and 2009 (9.9% vs 18% and 3.5% vs 7.7%, respectively). However, there was no significant difference between 2009 and 2019 (food sensitization, 18% vs 15.6%; confirmed FA, 7.7% vs 11.1%). Stable tendency are consistent with those in reports from United States, Australia, Britain, Canada, and Thailand.^{6-8,15-17} Therefore, we speculated that FA prevalence began to show a rapid rise in the 1990s, reaching a peak around 2010, and then remained stable in Chinese children. Before 2010, the rising prevalence may be related to gradual westernization of lifestyles and the competition with western industrialization. However, having the second largest Gross Domestic Product in the world since 2010, the living environment and lifestyles of Chinese people has not changed much. This may partly explain why FA prevalence has stabilized in the past decade. However, it should be noted that even though the FA prevalence in 2009-2019 was not statistically significant, it did increase by approximately 44%. There may be other reason for the slow but continuous rise in FA prevalence, which may continue to increase in the future. Therefore, the prevalence of FA should be continuously observed yearly.

Although only about 10% of the parent-reported FA cases were confirmed by OFC, the reported incidence of FA can provide public health information related to the diagnosis of FA. A Canadian study of parents who filled out a FA questionnaire by telephone found that although parents reported an increase of 7.1% and 8.7% of suspected allergies in children in 2010 and 2016, respectively, there was no difference in the prevalence of physician-confirmed allergies (5.9% vs 6.1%).⁸ Self-reported cases of FA in American adults also increased in 2001, 2006, and 2010, while the prevalence of confirmed FA did not increase significantly.¹⁸ However, contrary to the trend of changes in the prevalence of food sensitization and allergy, the prevalence of parent-reported FA did not change from 1999 to 2009 (13.7% vs 16.7%), but increased rapidly from 2009 to 2019 (16.7% vs 22.8%) in our three surveys. This indicated that, as in Western countries²⁻⁴, the awareness of FA among Chinese parents has increased in the past decade because of the increased levels of education and extensive health education. At the same time, parents may confuse allergic symptoms with those of lactose intolerance, irritable bowel syndrome, and other diseases; therefore, the real condition needs to be diagnosed by a professional allergist.

Although 90% of childhood FA are caused by eight foods, egg and milk have been the two top food allergens among children in Chongqing, China, since 1999. Peanut and tree nut allergies appear to be rare in Asia, possibly due to genetic background and different lifestyles,

such as Asians are more likely to eat boiled and scrambled peanuts instead of peanut butter¹⁹, which may reduce the allergenicity of peanut. The prevalence of egg allergy was the highest in both the 1999 and 2009 surveys, but it was lower than that of CMPA in the 2019 survey (5.0% vs 5.7%), and it did not change over the past 20 years. It is important to note that although the increase in the prevalence of CMPA was not statistically significant at 10-year intervals, its prevalence gradually overtook that of egg allergy, and it became the most common FA in children over a 20-year period. Thus, the increased prevalence of FA over a 20-year period may be associated with an increase in CMPA.

Epidemiological data show that environmental factors can change the course and characteristics of the disease through epigenetic effects.²⁰ From 1999-2009, in addition to the change in the prevalence rate, the symptoms of FA in children have also changed. According to the data, the children diagnosed with FA in 1999 and 2009 presented mainly with skin symptoms, while gastrointestinal symptoms were not common. In 2019, the proportion of children with FA presenting with gastrointestinal symptoms increased significantly, similar to that of skin symptoms. The change may have to do with that parents were more aware about abdominal mischief can be caused by allergies. The other reason is the improvement of scientific diagnostic criteria and medical methods may contribute to increase the diagnose rate of gastrointestinal diseases²¹. The majority of those with gastrointestinal symptoms were allergic to cow's milk. Therefore, cow's milk may be the main antigen that causes non-IgE-mediated FA in China.

Our study has several limitations. First, we conducted three surveys in the same clinic, there may be single-center deviation. Second, although we estimated the sample size during the study design phase, the small sample size led to limited statistical power and wide confidence intervals. Third, the few children who dropped out may have led to underestimation of the true prevalence. If we assume that the prevalence of FA in drop-out children is consistent with the diagnosed children, then the actual prevalence in the three studies were 4.6%, 9.1%, 12.1%, respectively. After completing our analyses, we came to the same conclusion.

In summary, the prevalence of FA in children rapidly increased after the 1990s and gradually stabilized after 2010 in Chongqing, China. Although egg and cow's milk remain the two top food allergens in children, since 2009 CMPA has replaced egg allergy as the most common FA in children. Moreover, though the prevalence of FA has not increased from 2009 to 2019, the prevalence of gastrointestinal symptoms as a manifestation of FA has increased, especially in CMPA, suggesting that further study of non-IgE mediated FA is required in the

future.

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Table I Prevalences of food sensitization and allergy, parent-reported FA over the last twenty years

	1999(N=314)	2009(N=401)	2019(N=513)	χ^2	P value
	No. (%)	No. (%)	No. (%)		
Parent-reported FA	43 (13.7)	67 (16.7)	117 (22.8) ^{†‡}	11.982	.003
Egg sensitization	23 (7.3)	62 (15.5) [§]	59 (11.5)	11.306	.004
Milk sensitization	10 (3.2)	25 (6.2)	27 (5.3)	3.501	.174
Positive SPT result	31 (9.9)	72 (18.0) [§]	80 (15.6) [‡]	9.405	.009
Positive FE result	21(6.7)	45(11.2) [§]	88(17.2) ^{†‡}	20.397	.001
Challenge-confirmed FA	11(3.5)	31 (7.7) [§]	57 (11.1) [‡]	14.803	.001
Egg allergy	9(2.9)	20 (5.0)	28 (5.5)	3.117	.210
CMPA	5(1.6)	14 (3.5)	29 (5.7) [‡]	8.827	.012
Multi-FA	4 (1.3)	3 (0.7)	7 (1.4)	0.819	.664

SPT: Skin prick test; CMPA: Cow's milk protein allergy; FA: Food allergy; FE: Food Elimination;

†: Pairwise comparison between 2009 and 2019, $p < 0.05$

‡: Pairwise comparison between 1999 and 2019, $p < 0.05$

§: Pairwise comparison between 1999 and 2009, $p < 0.05$

Table II Distribution of positive skin prick test (SPT) results in the three surveys

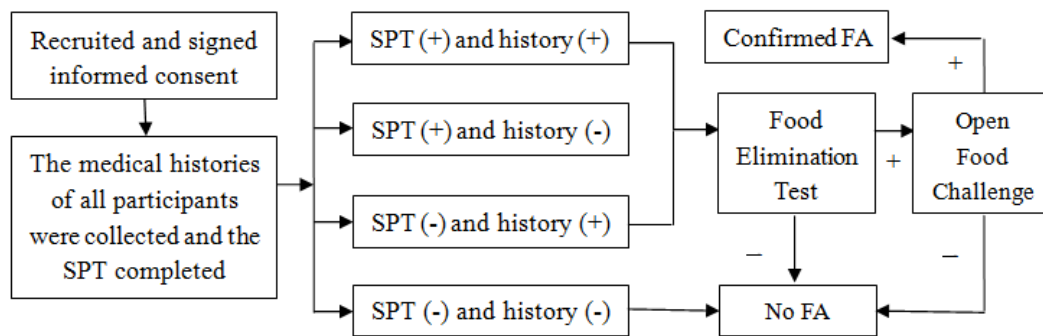
	Egg	Milk	Peanut	Fish	Orange	Wheat	Shrimp	Soy
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
1999	23(7.3)	10 (3.2)	1 (0.3)	1 (0.3)	3 (1.0)	1 (0.3)	0	3 (1.0)
2009	62 (15.5)	25 (6.2)	6 (1.5)	3 (0.7)	0	2 (0.5)	1 (0.2)	2 (0.5)
2019	59 (11.5)	27 (5.3)	2 (0.4)	3 (0.6)	3 (0.6)	0	0	0

Table III Clinical symptoms of Challenge-confirmed FA in the three surveys

	1999 (N=11)	2009 (N=31)	2019 (N=57)	
	No. (%)	No. (%)	No. (%)	P-value
Skin	10 (90.9)	27 (87.1)	33 (57.9)	.082
Gastrointestinal	2 (18.2)	4 (12.9)	25 (43.9) ^{†‡}	<.001
Respiratory	1 (9.1)	0	2 (3.51)	.473

[†]: Pairwise comparison between 2009 and 2019, p<0.05

[‡]: Pairwise comparison between 1999 and 2019, p<0.05



SPT:Skin Prick Test; FA:Food Allergy;+ : positive; -: negative;

Figure 1. Diagnostic process for food allergies in the three cross-sectional surveys (1999, 2009, and 2019)

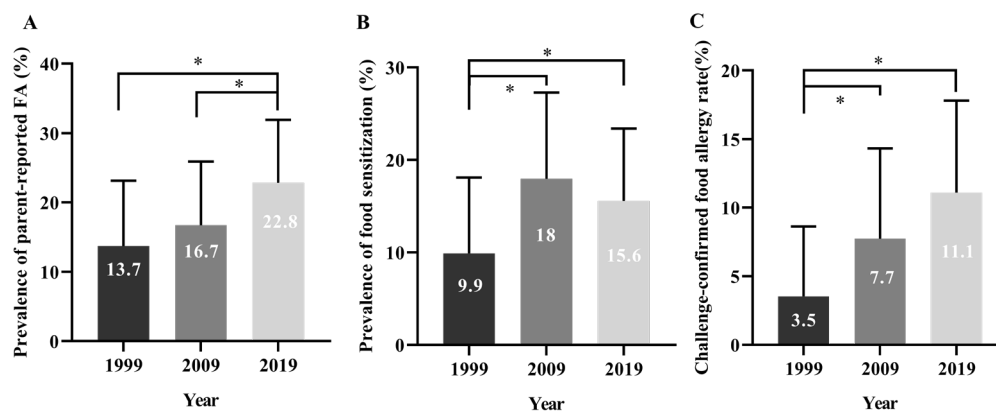


Figure2.Prevalence of food sensitization and allergy in the three surveys (1999, 2009, and 2019)

*Statistically significant differences:P < .05

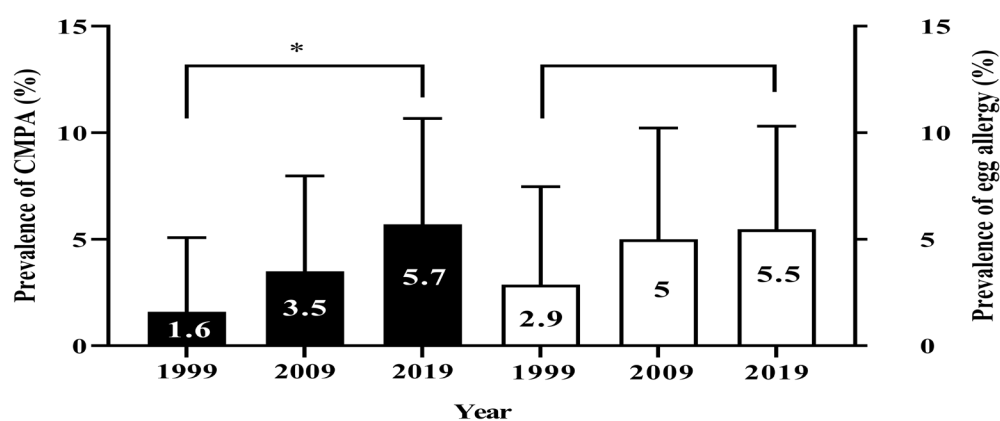


Figure 3. Prevalences of egg and cow's milk protein allergies in the three surveys (1999, 2009, and 2019)

*Statistically significant differences:P<0.05