

ORIGINAL ARTICLE

Food Allergy

Early food allergy and respiratory allergy symptoms and attention-deficit/hyperactivity disorder in Chinese children: A cross-sectional study

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Abstract

Background: The relationship between food allergy and respiratory allergy and attention-deficit/hyperactivity disorder (ADHD) in children is rarely investigated. The objective of this study was to determine whether early food allergy and respiratory allergy symptoms are associated with the prevalence of ADHD in Chinese school-age children.

Methods: This cross-sectional study was conducted in school-age children using cluster-stratified methods from 9 cities across China between November and December 2005. A family and social environmental questionnaire including the diagnosis history of ADHD and allergic diseases (food allergy, allergic rhinitis, and bronchial asthma), as well as general information, was completed by parents.

Results: The prevalence of both allergic rhinitis (20.4%) and asthma (11.6%) in the food allergy group was significantly higher than in the non-food allergy group (9.0% and 2.8%, respectively; both $P < .001$). The multivariable analysis showed that single food allergy (OR = 1.53, 95% CI: 1.13-2.05, $P = .005$), food allergy complicated with allergic rhinitis or asthma (OR = 3.36, 95% CI: 2.19-5.14, $P < .001$), and food allergy complicated with allergic rhinitis and asthma simultaneously (OR = 4.08, 95% CI: 2.05-8.11, $P < .001$) were independently associated with the increased risk of ADHD.

Conclusions: Early food allergy is associated with ADHD in school-age children. Early food allergy and respiratory allergy symptoms independently and synergistically contributed to higher risk of ADHD. Monitoring food allergy in early life could help in the early prediction and intervention for the consequent allergy march and ADHD in children.

KEYWORDS

allergy march, attention-deficit/hyperactivity disorder, food allergy, respiratory allergy

1 | INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in children and adolescents, which is characterized by inattention, hyperactivity, and impulsivity. The prevalence shows a peak in school-age children, but the symptoms of ADHD could persist into adolescence and adulthood.

The prevalence of allergic diseases and ADHD increased concurrently over the recent years. The overall prevalence of allergic diseases is as high as 25%,¹ and the prevalence of ADHD is 10%.² The pathogenesis of ADHD is still unclear. The available evidence suggests that ADHD is caused by multiple biologic factors (gene-environment interactions and abnormal brain development) and social-psychologic factors (psychologic behavioral factors, family-school-social factors) acting alone or synergistically.

It is widely accepted that ADHD is associated with imbalance among chemical neurotransmitters in the brain, including dopamine, norepinephrine, and 5-hydroxytryptamine. The deregulation of these neurotransmitters is also observed in allergic reactions, and some researchers speculated that allergy could be one of the risk factors of ADHD. Pelsser et al³ even speculated that ADHD is not caused by allergic reactions, but could be an allergic disease itself. Clinical studies have shown that allergic diseases and neurodevelopmental disorders are commonly concurrent, and the underlying mechanisms could be associated with various factors including genetic factors, neurotransmitter,⁴ neuroimmunity,⁵ and brain-gut communication.⁶

Previous studies on the associations between allergic diseases and childhood ADHD mainly focused on the allergic diseases with a single organ or system involved, such as allergic rhinitis, asthma, and eczema.⁶⁻⁸ However, the allergic reactions in a single organ or system could not reflect the effects of systemic immune responses on ADHD. Rich epidemiologic evidence suggests that there is a systematic sequence of atopic manifestations named allergy march, which usually begins with food allergy and is followed by respiratory allergies and atopic conjunctivitis.⁹

Food allergies are a group of digestive system or systemic immunologic diseases that share the same etiology. Food allergy is common in children younger than 1 year, and the peak incidence is at the age of 4-6 months. The exposure to food allergens in infants occurs much earlier than the exposure to inhaled allergens, and the manifestations of food allergies are also generally earlier than respiratory allergy. A recent birth cohort study showed evidence that food sensitization in early life increased the risk of subsequent asthma and allergic rhinitis.¹⁰ The processes of allergy march are also generally accompanied by behavioral and neuropsychologic disorders.^{11,12}

Nevertheless, few studies investigated the relationship between early food allergy and consequent respiratory allergy symptoms and ADHD. Therefore, this study aimed to investigate the associations between early food allergy with or without respiratory allergy and ADHD in school-age children.

2 | METHODS

2.1 | Study design and subjects

This cross-sectional study was conducted in school-age children in China. Considering the wide geographic distribution, imbalanced economic development, and numerous ethnicities, stratified cluster sampling was conducted to recruit the participants. Nine cities (Urumqi, Shihezi, Chengdu, Xi'an, Hohhot, Wuhan, Guangzhou, Shanghai, and Harbin) were finally included. The cluster-stratified method was conducted according to cities, districts, schools, grades, and classes.

The parents of the children were surveyed by questionnaires between November and December 2005. All these cities were with relatively sufficient healthcare sources and high public awareness of allergic diseases and ADHD, and the healthcare providers in these cities abided by the national standards to diagnose diseases; thus, the previous diagnosis and data of potential factors were reliable.

Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine approved the ethical aspects of this study (No. XHEC-D-2017-047).

2.2 | Survey

The objectives of this study were explained to the principals and teachers of the selected schools by the investigators. After obtaining the permission from the schools, children were asked to bring the questionnaire and supplementary files (including the objectives and instructions of this questionnaire survey) to their parents. The parents were informed that the participation in this survey was of their own free will and were ensured of the anonymity. Eligible students were those aged 5-12 years (grades 1-6) and studying in the selected schools.

This questionnaire has been shown to be valid and reliable and has been used in a number of studies.^{13,14} Each copy of the questionnaire was attached with a copy of the informed consent. A self-designed questionnaire was used, which included gender, age, perinatal factors (delivery mode, gestational weeks, and feeding patterns), family environmental factors (education level of the caregivers, family income, marital status of the parents, and geographic location), and diagnosis history of diseases (ADHD, food allergy, allergic rhinitis, and asthma).

Attention-deficit/hyperactivity disorder was diagnosed according to the answers (Yes or No) to the question "Has the child been clearly diagnosed by a specialist physician (a developmental behavioral pediatrician or psychiatrist) with ADHD?" by the parents. Food allergy was diagnosed according to the answers (Yes or No) to the question "Has the child been clearly diagnosed by a specialist physician (physician from the department of children's health prevention or immunology) with food allergy?" Similarly, allergic rhinitis and asthma were also diagnosed by a parent-reported dichotomous question. All the investigators conducting the questionnaire survey and data input process were uniformly trained.

TABLE 1 Comparison of the general characteristics and food allergy between ADHD and non-ADHD children

Variable	N ^a	ADHD (n = 979)	Non-ADHD (n = 21 021)	P
Age (y)	21 871	8.8 ± 1.7	8.8 ± 1.8	.747
Gender				
Male	21 890	655 (67.5)	10 214 (48.8)	<.001
Female		315 (32.5)	10 706 (51.2)	
Gestational weeks				
Preterm delivery	21 524	81 (8.5)	1135 (5.5)	<.001
Term delivery		802 (84.6)	18 220 (88.5)	
Post-term delivery		65 (6.9)	1221 (5.9)	
Delivery mode				
Spontaneous delivery	21 907	651 (66.8)	13 103 (62.6)	<.001
Forceps delivery		69 (7.1)	993 (4.7)	
Cesarean section		255 (26.2)	6836 (32.7)	
Feeding pattern				
Breast-feeding	21 963	649 (66.5)	13 781 (65.7)	.803
Mixed feeding		194 (19.9)	4354 (20.7)	
Artificial feeding		133 (13.6)	2852 (13.6)	
Education degree of the caregivers				
Illiteracy	21 774	23 (2.4)	278 (1.3)	<.001
Elementary or junior middle school		395 (40.8)	5335 (25.6)	
Senior middle school or technical secondary school		138 (14.3)	6863 (33.0)	
Junior college or college		107 (11.1)	4059 (19.5)	
Higher than college		1135 (5.5)	4272 (20.5)	
Family income per capita/mo				
<800	21 740	290 (30.2)	4046 (19.5)	<.001
800-1500		378 (32.9)	6866 (33.0)	
1500-2500		185 (19.3)	4889 (23.5)	
>2500		170 (17.7)	4978 (24.0)	
Relation between the parents				
Harmony	21 831	795 (82.3)	19 096 (91.5)	<.001
Quarrel frequently		90 (9.3)	661 (3.2)	
Separated		17 (1.8)	269 (1.3)	
Divorced		55 (5.7)	748 (3.6)	
Remarried		9 (0.9)	91 (0.4)	
Geographic location				
Shanghai	22 000	158 (16.1)	4232 (20.1)	<.001
Guangzhou		95 (9.7)	2997 (14.3)	
Xi'an		63 (6.4)	1589 (7.6)	
Wuhan		159 (16.2)	1900 (9.0)	
Chengdu		113 (11.5)	2733 (13.0)	
Harbin		132 (13.5)	2769 (13.2)	
Hohhot		79 (8.1)	1948 (9.3)	
Urumqi		121 (12.4)	1913 (9.1)	
Shihezi		59 (6.0)	940 (4.5)	
Food allergy	1228	101 (10.3)	1127 (5.4)	<.001

^aThe number of missing values was different for different questions; thus, the number of effective cases was also different in different groups.

2.3 | Statistical analysis

SPSS 21.0 (IBM, Armonk, NY, USA) was used for statistical analysis. Categorical data are presented as frequencies and were analyzed with the chi-square test. Continuous data are presented as mean $\pm$ standard deviation and were analyzed with the Student *t* test or analysis of variance with the Tukey post hoc test, as appropriate. The factors with statistical significance in the univariable analyses were included as independent factors in multivariable binary logistic regression model along with ADHD as the dependent factor. Two-sided *P*-values $<.05$ were considered statistically significant. A complete data analysis was performed, and subjects with missing data were excluded.

3 | RESULTS

3.1 | Participants

A total of 23 791 questionnaires were delivered to the children, and 22 018 questionnaires were recovered. The effective response rate was 92.5%. Among these children, there were 10 869 boys and 11 021 girls (128 missing data for gender). Mean age was 8.8 ± 1.8 years.

3.2 | Comparison of the general characteristics and food allergy between ADHD and non-ADHD children

Age and feeding patterns were not significantly different between the 2 groups ($P > .05$). The ADHD group included more boys (67.5% vs 48.8%, $P < .001$), more preterm children (8.5% vs 5.5%, $P < .001$), more forceps delivery (7.4% vs 4.7%, $P < .001$), lower education degree of the caregivers ($P < .001$), lower family income ($P < .001$), and more frequent parental discord ($P < .001$). The geographic location was also related to the incidence of ADHD ($P < .001$). The prevalence of food allergy was 5.4% and 10.3% in the non-ADHD group and the ADHD group, respectively ($P < .001$; Table 1).

3.3 | Concurrent respiratory allergy in children with food allergy

The children were categorized into the food allergy ($n = 1228$) and non-food allergy ($n = 20\,761$) groups. The results showed that the prevalence of both allergic rhinitis (20.4%) and asthma (11.6%) in the food allergy group was significantly higher than in the non-food allergy group (9.0% and 2.8%, respectively; both $P < .001$; Table 2).

The children were further categorized into no food allergy group, single food allergy group (FA group), food allergy complicated with 1 respiratory allergy group (FA + AR/BA group), and food allergy complicated with 2 respiratory allergies group (FA + AR + BA group). Among the 1228 children with food allergy, 920 were in the FA group (74.9%), 227 were in the FA + AR/BA group (18.5%), and 81 were in the FA + AR + BA group (6.6%; Figure 1A). 25.1% of the children with food allergy were complicated with respiratory allergy symptoms.

Compared with the prevalence of ADHD in children without food allergy (4.2%), it was significantly higher in the FA group (6.7%). The prevalence of ADHD was even higher in the FA + AR/BA group (12.4%) and was the highest in the FA + AR + BA group (14.8%; all $P < .001$ vs the no food allergy group; Figure 1B).

3.4 | Association between allergic diseases and ADHD by multivariable analysis

A multivariable analysis was carried out to investigate the associations between food allergy with or without respiratory allergy and ADHD in children. The results (Table 3) showed that female (OR = 0.49, 95% CI: 0.43-0.57, $P < .001$), living in Wuhan (OR = 1.71, 95% CI: 1.32-2.22, $P < .001$), living in Harbin (OR = 1.36, 95% CI: 1.05-1.77, $P = .02$), living in Urumqi (OR = 1.60, 95% CI: 1.23-2.09, $P = .001$), living in Shihezi (OR = 1.46, 95% CI: 1.04-2.04, $P = .03$), term delivery (OR = 0.64, 95% CI: 0.50-0.82, $P < .001$), higher-than-college education of the caregivers (OR = 0.48, 95% CI: 0.28-0.80, $P = .005$), parents quarreling frequently (OR = 2.72, 95% CI: 2.12-3.48, $P < .001$), divorced parents (OR = 1.76, 95% CI: 1.31-2.37, $P < .001$), remarried parents (OR = 2.25, 95% CI: 1.11-4.55, $P = .02$), FA group (OR = 1.53, 95% CI: 1.13-2.05, $P = .005$), FA + AR/BA group (OR = 3.36, 95% CI: 2.19-5.14, $P < .001$), and FA + AR + BA group (OR = 4.08, 95% CI: 2.05-8.11, $P < .001$) were independently associated with the increased risk of ADHD (Table 3).

4 | DISCUSSION

Food allergy is a common chronic disorder in infancy. In a previous study by our group, the prevalence of food allergy among infants aged 0-24 months in Chongqing, China, increased from 3.5% in 1999 to 7.7% in 2009, suggesting that the prevalence of food allergy increased 1-fold over a decade.¹⁵ The first occurrence of food allergy is mainly during infancy. A meta-analysis study found that in the first year of life, there is the onset of food allergy in 79.8% of babies. Asthma starts later, in the first year of life in 41.8%, and within the eighth year in 92.5%. Allergic rhinitis begins in 35% in the first year and in 59% by age 5.¹⁶ Therefore, we defined early food allergy based on the evidence from past epidemiologic studies.¹⁷

Early food allergy could increase the risk of respiratory allergy such as allergic rhinitis¹⁸ and asthma.¹⁹ Penard-Morand et al²⁰ reported that asthma and allergic rhinitis are positively associated with food allergy and hyper-responsiveness to food allergens in infancy. A recent prospective multicenter study provided evidence of respiratory allergy march in Chinese children.²¹ In the present study, the risk of allergic rhinitis and asthma increased 2.6- and 4.5-fold, respectively, in children with food allergy. In addition, over one-fourth of the food-allergic children were complicated with respiratory allergy symptoms, supporting that food allergy in early life plays an important role in consequent respiratory allergy.

Food allergy in early infancy could not only result in the march to other allergic diseases, but might also promote the development

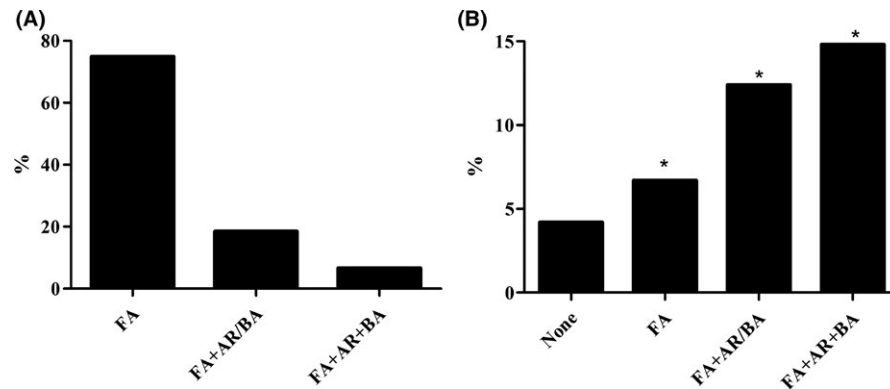


FIGURE 1 A, Proportion of children in different food allergy groups. B, Frequency of ADHD according to the groups of food allergy. Groups: no food allergy group; single food allergy group (FA group); food allergy complicated with 1 respiratory allergy group (FA + AR/BA group); and food allergy complicated with 2 respiratory allergies group (FA + AR + BA group). * $P < .001$ vs the no food allergy group

Variable	Allergic rhinitis n (%)		Asthma n (%)	
	Yes	No	Yes	No
No food allergy	1870 (9.0)	18 887 (91.0)	589 (2.8)	20 179 (97.2)
Food allergy	251 (20.4)	977 (79.6)	142 (11.6)	1086 (88.4)
P	<.001		<.001	
OR (95% CI)	2.595 (2.241-3.004)		4.480 (3.693-5.434)	

TABLE 2 Concurrent respiratory allergy in children with or without food allergy

of neurodevelopmental diseases. The main symptoms of early food allergy include gastrointestinal symptoms and skin symptoms, but could also involve damages to multiple systems such as respiratory, immune, circadian, and nervous system. Food allergy might be a risk factor for neurodevelopmental and behavioral disorders in children, which is supported by a recent study in which the risk of ADHD was increased in adolescents with food allergy (OR = 3.14).²²

The allergy march symptoms were found to increase the effects of food allergy on the development of children. The present study suggests that the respiratory allergy symptoms were associated with the increased risk of ADHD with OR = 3.36 and OR = 4.08 for children with food allergy complicated with 1 or 2 respiratory allergies. These findings suggest that respiratory allergy could synergistically interact with food allergy and was associated with the increased risk of ADHD in children.

There are 3 possible explanations on the relationship between early allergic diseases and neurodevelopmental disorders. The first is the shared genetic factors between allergic diseases and ADHD. Both ADHD and allergic diseases are highly heritable. Past studies found some genes involved in the regulation of immune system may also play a role in the development of ADHD symptoms. For example, STAT6 gene is closely related to allergic diseases²³ and is highly expressed in the central nervous system, which may be implicated in the pathogenesis of ADHD.²⁴ The more allergic diseases, the greater the possibility of related genetic variants. The second is the effects of inflammatory cytokines on the development of the brain. In early stages of life, the immune system is not mature yet,

and children with allergic diseases may be exposed to high levels of inflammatory cytokines, which are released after allergic sensitization. These cytokines could pass the blood-brain barrier and activate the ADHD-related pathways and neuroimmune mechanisms, and induce structural and functional damages in brain development.^{25,26} The third is the sleep problems caused by allergic diseases. A previous study demonstrated that several ADHD-related chemical neurotransmitters play important roles in the regulation of sleep rhythm.²⁷ Allergic children are commonly with sleep problems. The persistent existence of such sleep disorders could increase or regulate the risk of neurodevelopmental disorders (such as ADHD).²⁸ Food allergy and respiratory allergy could synergistically increase potential sleep problems and be associated with higher risk of ADHD.

In addition to allergy, some other adverse environmental factors could also influence the risk of ADHD. The geographic effect for ADHD was interesting. Compared with Shanghai, Wuhan (OR = 1.71), Harbin (OR = 1.36), Urumqi (OR = 1.60), and Shihezi (OR = 1.46) were associated with higher risk of ADHD. However, we did not find interactive effect between allergy and location ($P = .66$) in our data, which meant allergy and residence location was associated with the risk of ADHD independently but no allergy $\times$ location effect on ADHD. The geographic variation in ADHD may come from many factors, such as solar intensity,²⁹ healthcare supply,³⁰ economic development, public awareness of ADHD, and environmental contamination. Future studies should subdivide geographic factors to investigate the mechanism that is important for individualized prevention and intervention of ADHD.

TABLE 3 Comparison of the effects of food allergy and respiratory allergy symptoms on the risks of ADHD in children (n = 20 684)

	P	Odds ratio	95% CI	
			Lower limit	Upper limit
Gender (male as the reference)	<.001	0.493	0.427	0.569
City (Shanghai as the reference)	<.001			
Guangzhou	.582	0.926	0.705	1.217
Xi'an	.513	1.115	0.804	1.546
Wuhan	<.001	1.714	1.323	2.220
Chengdu	.257	1.163	0.896	1.511
Harbin	.021	1.360	1.048	1.765
Hohhot	.841	0.969	0.714	1.316
Urumqi	.001	1.600	1.225	2.090
Shihezi	.028	1.457	1.041	2.041
Gestational weeks	.002			
(preterm as the reference)				
Term	<.001	0.642	0.501	0.823
Post-term	.119	0.757	0.533	1.075
Delivery mode	.021			
(spontaneous as the reference)				
Forceps	.059	1.313	0.990	1.742
Cesarean	.098	0.871	0.740	1.026
Education degree of the caregivers	<.001			
(illiteracy as the reference)				
Elementary or junior middle school	.481	1.187	0.736	1.913
Senior middle school or technical secondary school	.367	0.800	0.493	1.298
Junior college or college	.087	0.644	0.389	1.066
Higher than college	.005	0.476	0.284	0.798
Family income	.059			
(<800/mo as the reference)				
800-1500/mo	.012	0.796	0.665	0.952
1500-2500/mo	.054	0.810	0.653	1.004
>2500/mo	.407	0.903	0.709	1.149
Marital relations	<.001			
(harmony as the reference)				
Quarrel frequently	<.001	2.717	2.120	3.480
Separated	.298	1.327	0.779	2.262
Divorced	<.001	1.761	1.311	2.365
Remarried	.024	2.250	1.113	4.546
Food allergy group (non-food allergy as the reference)	<.001			
FA group	.005	1.526	1.134	2.053
FA + AR/BA group	<.001	3.357	2.191	5.143
FA + AR + BA group	<.001	4.076	2.049	8.105

In the present study, stratified cluster sampling was used to select the participants, which include over 20 000 school-age children from different schools in 9 major cities across China. Such large sample size

and good representativeness allow the results to reflect the overall prevalence of food allergy and ADHD in Chinese school-age children. Nevertheless, there are several limitations. First, the data from

rural areas and small or middle cities are lacking. Secondly, parent-reported diagnosis data could be biased. For example, the gold standard for diagnosing a food allergy is double-blind, placebo-controlled food challenge. If we want to define allergic diseases accurately, the improvement of measurements is necessary. Thirdly, the onset of allergic diseases was not involved in the measurements; although rich longitudinal evidence shows that food allergy mainly begins to occur during infancy and is the initiation of allergy march, we could not exclude the possibility of some later-onset food allergy in our samples. Fourthly, the severity of ADHD and allergic diseases in the children was not evaluated; thus, the exact effect power (eg, severity) of the allergic diseases on ADHD could not be correctly evaluated. Finally, due to the cross-sectional design, the present study could not show any causal relationship between food allergy and ADHD. Future longitudinal studies are needed to elucidate the effects and underlying mechanisms of food allergy and respiratory allergy on neurodevelopmental disorders in children.

Early food allergy is associated with ADHD in school-age children. The respiratory allergy symptoms are associated with increased risk of ADHD in children with food allergy. For high-risk children with food allergy, behavioral monitoring and interventions could help reducing the consequent respiratory allergy and might decrease the risks of the consequent ADHD in children at the same time. The findings of the present study could provide clues for the prevention and early intervention of ADHD in children.

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CONFLICT OF INTEREST

All authors declare that they have no competing interests.

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