

Asthma, Rhinitis, and Skin Test Reactivity to Aeroallergens in Families of Asthmatic Subjects in Anqing, China

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In industrialized countries with a Western lifestyle, sensitization to perennial aeroallergens is strongly associated with asthma, whereas sensitization to seasonal aeroallergens is closely related to allergic rhinitis. Little is known, however, about the relation between skin test reactivity to aeroallergens and either asthma or rhinitis in mainland China. We studied 10,009 members of 2,544 families in Anqing (China) that were selected on the basis of physician-diagnosed asthma in at least two siblings. Generalized estimating equations were employed to study the association between skin test reactivity to aeroallergens and either asthma or rhinitis. After adjustment for age, sex, intensity of smoking, skin test reactivity to other aeroallergens, and household correlations, sensitization to dust mite was an independent predictor of both asthma (OR = 1.3, 95% CI = 1.1 to 1.5, $p = 0.008$) and rhinitis (OR = 1.3, 95% CI = 1.0 to 1.8, $p = 0.04$). Sensitization to mold was significantly associated with asthma (OR = 1.6, 95% CI = 1.1 to 2.3, $p = 0.008$), and sensitization to silk was an independent predictor of rhinitis (OR = 1.5, 95% CI = 1.1 to 2.2, $p = 0.02$). Although 46.9% of the study participants were sensitized to at least one allergen, only 3.5% of study subjects reported nasal symptoms consistent with rhinitis. Among asthmatic subjects, 6.2% reported nasal symptoms. Whereas sensitization to perennial aeroallergens was associated with asthma among families of asthmatic subjects in rural China, sensitization to silk was the strongest predictor of rhinitis in this population. Our findings also suggest that allergic rhinitis is far less common among asthmatic subjects in rural China than in asthmatic subjects in industrialized countries with a Western lifestyle.

Asthma, a major public health problem, affects more than 17 million people in the United States (1). The prevalence of asthma has increased in the United States and worldwide (2–7), and a parallel increase in the prevalence of hay fever has been observed in the United Kingdom and Australia (5, 6, 8). Current epidemiologic data suggest that asthma and allergic rhinitis are less common in China than in Western countries (9–11).

In most studies conducted in industrialized countries, skin test reactivity to perennial aeroallergens is strongly associated with asthma (12–17), whereas skin test reactivity to pollen is more closely correlated with allergic rhinitis (16–17). Little is

known, however, about the relation between skin test reactivity to aeroallergens and either asthma or allergic rhinitis in mainland China (11, 18). We were interested in examining the relation among asthma, allergic rhinitis, and skin test reactivity to aeroallergens in 10,009 subjects from 2,544 families of asthmatics living in a predominantly rural environment in the province of Anqing.

METHODS

A description of the study site and details of methods for selection of the study subjects have been reported (19). Anqing has three urban areas and eight rural counties, with a total area of 15,000 km². The total population in 1990 was 5.8 million (urban, 9%; rural, 91%). Asthma families from the eight counties of Anqing (Zongyang, Huining, Qianshan, Tongcheng, Taihu, Wangjiang, Susong, and Yuengsi) were enrolled in this genetic epidemiology study through a multistage process (19). For a family to be eligible, patients with physician-diagnosed asthma had to have a history of repeated onset of wheeze with dyspnea but be asymptomatic between two events and have respiratory symptoms that were relieved by bronchodilator use. The following criteria were used for inclusion of asthma families in the study: (1) at least two siblings ≥ 6 yr of age with physician-diagnosed asthma, (2) both parents available, and (3) no more than one parent with physician-diagnosed asthma.

Procedures

Letters explaining the purpose of the study were sent to all eligible families. Local officials and health centers arranged for appointments to take place at a central office at a time convenient for the participants. Data were collected by faculty members from Anhui Medical University and by trained interviewers between July 1, 1994 and January 26, 1998.

Unless otherwise specified, the following procedures were carried out in accordance with the NIH Collaborative Agreement on Asthma Genetics: (1) completion of a standardized questionnaire (modified ATS-DLD), including questions on respiratory symptoms, respiratory health status, occupational history, tobacco use, home environment, and family history of asthma and other chronic diseases; (2) pulmonary function testing (spirometry); (3) methacholine challenge testing, using the Chatham protocol (20), for subjects whose FEV₁ was $> 60\%$ of predicted; (4) bronchodilator testing; (5) skin testing of reactivity to 10 allergens along with a positive and a negative control; and (6) collection of blood samples for serum total IgE level and DNA extraction. In addition, height and weight were measured by standard methods; subjects removed their shoes and outerwear before measurement. Height was measured to the nearest 0.1 cm on a portable stadiometer. Weight was measured to the nearest 0.1 kg with the subject standing motionless on the scale.

Spirometry

Pulmonary function tests were performed with ATS "Snowbird Guideline" approved criteria (Schiller, Baar, Switzerland) and with subjects seated and wearing noseclips. As many as eight attempts were made by each participant to obtain three acceptable measures. Spirometry was performed according to ATS specifications; the FEV₁/FVC from the best test effort and the highest FEV₁ value are reported (21).

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TABLE 1. COMPARISON OF SUBJECTS WITH AND WITHOUT COMPLETE INFORMATION ON AIRWAY RESPONSIVENESS TO METHACHOLINE AND SKIN TEST REACTIVITY TO AEROALLERGENS IN ANQING, CHINA

Characteristics	Information on Airway Responsiveness to Methacholine and STR to Aeroallergens	
	Complete*	Incomplete*
Number	10,009	2,988
Sex, male:female	4,862:5,147 [†]	1,532:1,456
Age, yr	30.1 ± 15.5 [‡]	36.9 ± 18.0
Former/current cigarette smoking, n (%)	3,062 (31.0) [‡]	855 (33.4)
Physician-diagnosed asthma, n (%)	1,854 (19.0) [‡]	1,046 (41.4)
FEV ₁ /FVC < 0.75 n (%)	2,695 (26.9) [‡]	2,199 (73.6)
Report of wheezing, n (%)	3,145 (31.5) [‡]	1,340 (52.2)
Airways hyperresponsiveness to methacholine, n (%) [‡]	3,302 (33.0) [‡]	226 (44.0)
STR to ≥ one allergen, n (%)	4,698 (46.9) [‡]	632 (49.5)
Serum total IgE (geometric mean, IU/ml)	142.1	139.7

Definition of abbreviations: STR = skin test reactivity.

* Percentages may reflect fluctuations in the denominator because of missing values.

[†] Indicates $p < 0.05$ compared with subjects without complete information.

[‡] Fall in FEV₁ of at least 20% after the administration of ≤ 25 mg/ml of inhaled methacholine.

Spirometry was repeated 10 min after subjects inhaled 180 µg (two puffs) of albuterol using a spacer device.

Allergy Skin Testing

Skin testing was performed with a slightly modified version of the semiquantitative puncture method developed by Santilli and colleagues (22). In addition to histamine and saline controls, the following antigens were applied to the skin of the forearm: cockroach, house dust, mixed trees, mixed grasses, tobacco leaf, polyvalent molds, *Dermatophagoides pteronyssinus*, *D. farinae*, artemisia, and silk. A test was considered positive if the diameter of the skin wheal was ≥ 3 mm.

Measurement of Serum Total Immunoglobulin E Levels

Serum total IgE levels were determined by means of the UniCAP 100 system (Pharmacia & Upjohn, Kalamazoo, MI). All values were trans-

TABLE 2. NUMBER (PERCENTAGE) OF SUBJECTS WITH ASTHMA, RHINITIS, RESPIRATORY SYMPTOMS, AND NASAL SYMPTOMS AMONG 10,009 STUDY PARTICIPANTS IN ANQING, CHINA

Characteristics	n (%)*
Respiratory symptoms	
0	3,952 (39.5)
1	2,792 (27.9)
2	1,469 (14.7)
3	1,176 (11.7)
4	620 (6.2)
Asthma	842 (8.4)
Ever had hay fever	44 (0.4)
Ever nasal congestion without a cold	356 (3.6)
Rhinitis	348 (3.5)
Positive skin tests to aeroallergens, n	
0	5,311 (53.1)
1	1,496 (14.9)
2	1,113 (11.1)
3	879 (8.8)
4	478 (4.8)
5	311 (3.1)
6	189 (1.9)
7–8	163 (1.6)
≥ 9	69 (0.6)
Serum Total IgE > 100 IU/ml	1,917 (61.3)

* Percentages may reflect fluctuations in the denominator because of missing values.

formed to a log₁₀ scale for analysis, in accordance with the recognized logarithmic distribution of serum total IgE levels in the general population (23).

Definitions of Asthma and Rhinitis

Our definition of asthma was based on the presence of all of the following: affirmative answers to the questions “Do you have asthma?” and “Has your asthma been confirmed by a doctor?”; ≥ two respiratory symptoms (cough, wheezing, dyspnea, or nocturnal cough/wheezing/dyspnea) or history of recurrent asthma attacks; and airway hyperresponsiveness to methacholine, defined as a ≥ 20% fall in FEV₁ from baseline after administration of ≤ 25 mg of methacholine/ml. The presence of allergic rhinitis (hereafter referred to simply as rhinitis) was determined by affirmative answers to the questions “Have you had a stuffy nose without a cold?” and “Have you had a stuffy nose in the last 12 months?”.

Definition of Other Predictor Variables

Age, a potential confounder of the relationship between sensitization to allergens and asthma, was divided into four categories: 6–14, 15–34, 35–54, and ≥ 55 yr of age. The intensity of cigarette smoking in pack-years was calculated as the product of the period of tobacco use (in years) and the average number of cigarettes smoked per day, which was divided by 20 to convert to packs.

Statistical Methods

Bivariate relationships between predictor and outcome variables were analyzed using chi-square tests in the case of pairs of categorical variables or two-tailed *t* tests in the case of a categorical and a continuous variable. To account for correlations between individual subjects from the same household, methods developed by Zeger and Liang (24) with generalized estimating equations (GEEs) for the logistic case were used to evaluate the relationship between the dependent and the independent variables. All of the analyses were performed with the SAS statistical software package (SAS Institute, Inc., Cary, NC).

RESULTS

Subject Characteristics

The study originally included 12,997 subjects in 2,756 asthmatic families in Anqing, China. The present analyses were limited to the 10,009 subjects who had complete information on airway responsiveness to methacholine and skin test reactivity to aeroallergens. A comparison of the current study subjects with 2,988 subjects for whom information was missing is presented in Table 1. Subjects lacking information on airway responsiveness to methacholine ($n = 2,473$) and/or skin test reactivity to aeroallergens ($n = 1,711$) were older and had more severe airflow obstruction than did those who had complete information.

The percentage of subjects with asthma, rhinitis, respiratory and nasal symptoms among the 10,009 subjects included in the current study is shown in Table 2.

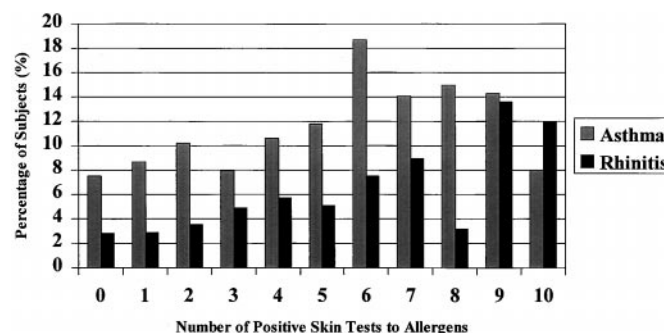


Figure 1. Asthma and rhinitis in relation to skin test reactivity to aeroallergens.

TABLE 3. RELATION BETWEEN SKIN TEST REACTIVITY (STR) TO AEROALLERGENS AND ASTHMA

Predictor	Asthma n (%) [*]	Odds Ratio (95% CI)
Positive skin tests		
0	387 (7.5)	1.0
1–5	389 (9.3)	1.3 (1.1–1.5)
> 5	66 (16.0)	2.3 (1.7–3.1)
STR to		
<i>D. pteronyssinus</i>		
No	548 (7.9)	1.0
Yes	294 (10.5)	1.4 (1.2–1.6)
<i>D. farinae</i>		
No	624 (8.1)	1.0
Yes	218 (10.9)	1.4 (1.2–1.6)
Mixed tree pollen		
No	769 (8.4)	1.0
Yes	73 (11.6)	1.4 (1.1–1.8)
Mixed grass pollen		
No	761 (8.5)	1.0
Yes	81 (10.9)	1.3 (1.0–1.7)
Artemisia		
No	771 (8.4)	1.0
Yes	71 (13.1)	1.7 (1.3–2.1)
Silk		
No	726 (8.3)	1.0
Yes	116 (11.6)	1.4 (1.2–1.8)
Mold		
No	790 (8.4)	1.0
Yes	52 (14.7)	1.9 (1.4–2.5)
Tobacco leaf		
No	753 (8.3)	1.0
Yes	89 (12.3)	1.5 (1.2–2.0)
House dust [†]		
No	723 (8.2)	1.0
Yes	119 (13.4)	1.7 (1.4–2.1)

^{*} Percentages may reflect fluctuations in the denominator because of missing values.

[†] Crude extract of house dust.

TABLE 4. RELATION BETWEEN SKIN TEST REACTIVITY (STR) TO AEROALLERGENS AND RHINITIS

Predictor	Rhinitis n (%) [*]	Odds Ratio (95% CI)
Positive skin tests, n		
0	146 (2.8)	1.0
2	39 (3.5)	1.3 (1.2–1.5)
4	27 (5.7)	1.8 (1.5–2.2)
10	3 (12.0)	4.3 (2.7–7.1)
STR to		
<i>D. pteronyssinus</i>		
No	214 (3.0)	1.0
Yes	134 (4.7)	1.6 (1.3–2.0)
<i>D. farinae</i>		
No	234 (3.0)	1.0
Yes	114 (5.6)	1.9 (1.5–2.4)
House dust		
No	291 (3.2)	1.0
Yes	57 (6.3)	2.0 (1.5–2.7)
Mixed tree pollen		
No	305 (3.3)	1.0
Yes	43 (6.8)	2.1 (1.5–3.0)
Mixed grass pollen		
No	304 (3.3)	1.0
Yes	44 (5.8)	1.8 (1.3–2.5)
Silk		
No	279 (3.1)	1.0
Yes	69 (6.7)	2.2 (1.7–2.9)
Mold		
No	323 (3.4)	1.0
Yes	25 (6.9)	2.1 (1.4–3.2)
Cockroach		
No	227 (3.2)	1.0
Yes	121 (4.2)	1.3 (1.1–1.6)
Tobacco leaf		
No	296 (3.2)	1.0
Yes	52 (7.1)	2.3 (1.7–3.1)

^{*} Percentages may reflect fluctuations in the denominator because of missing values.

Bivariate Analyses of the Relations among Skin Test Reactivity to Aeroallergens, Asthma, and Rhinitis

The relationship between asthma and skin test reactivity to aeroallergens in our study population is shown in Figure 1 and Table 3. With the exception of cockroach ($p = 0.09$), sensitization to any of the aeroallergens examined was significantly associated with asthma (Table 3).

We observed a linear relationship between rhinitis and the number of positive skin tests to aeroallergens (Figure 1 and Table 4). With the exception of artemisia ($p = 0.10$), skin test reactivity to any of the aeroallergens examined was significantly associated with rhinitis (Table 4). Because sensitization to house dust was strongly correlated with sensitization to dust mite and cockroach, we chose not to include house dust in the multivariate analyses.

Rhinitis was present in 6.2 and 3.2% of asthmatic and non-asthmatic subjects, respectively. Subjects who had rhinitis had 1.9 times higher odds of having asthma than did those without rhinitis (95% CI for OR = 1.4 to 2.6).

Multivariate Analysis of the Relation among Skin Test Reactivity to Aeroallergens, Asthma, and Rhinitis

After adjustment for age, sex, intensity of smoking, skin test reactivity to other aeroallergens, and household correlations using GEEs, sensitization to dust mite and sensitization to mold were independent predictors of asthma in our study population (Table 5). These results did not appreciably change if two alternative definitions of asthma (airway responsiveness to ≤ 8 mg/ml of methacholine and either two or more respira-

tory symptoms or history of asthma attacks; physician-diagnosed asthma and either two or more respiratory symptoms or history of asthma attacks) were employed.

In a multivariate analysis using GEEs, sensitization to dust mite and sensitization to silk were independent predictors of rhinitis (Table 5).

DISCUSSION

We found a very low percentage of subjects with rhinitis in a study of 10,009 members of 2,544 families of asthmatic subjects in Anqing, a predominantly rural province of China. After adjustment for potential confounders and skin test reactivity to other aeroallergens, sensitization to dust mite (*Der p I* or *Der f I*) was significantly associated with both asthma (OR = 1.3, 95% CI = 1.1 to 1.5, $p = 0.008$) and rhinitis (OR = 1.3, 95% CI = 1.0 to 1.8, $p = 0.04$). In multivariate analyses, sensitization to mold was associated with asthma (OR = 1.6, 95% CI = 1.1 to 2.3, $p = 0.008$), and sensitization to silk was an independent predictor of rhinitis (OR = 1.5, 95% CI = 1.1 to 2.2, $p = 0.02$).

Allergic rhinitis is one of the most common chronic allergic respiratory disorders in countries with a Western lifestyle (25, 26). Clinicians in industrialized countries have long been aware that allergic rhinitis and asthma commonly coexist (27), and studies conducted in Western countries have shown that nasal symptoms are reported in 28 to 78% of patients with asthma (27–29). In contrast, only 6.2% of asthmatic subjects in our study reported nasal symptoms suggestive of allergic rhinitis.

TABLE 5. PREDICTORS OF ASTHMA AND RHINITIS ON MULTIVARIATE REGRESSION ANALYSIS

	OR (95% CI)	p Value
Asthma*		
Age, yr		
6–14	1.0	
15–34	0.3 (0.3–0.4)	< 0.001
35–54	0.4 (0.4–0.5)	< 0.001
≥ 55	0.3 (0.2–0.4)	< 0.001
Skin test reactivity (STR) to dust mite†		
No	1.0	
Yes	1.3 (1.1–1.5)	0.008
STR to mold		
No	1.0	
Yes	1.6 (1.1–2.3)	0.008
Rhinitis*		
Age, yr		
5–14	1.0	
15–34	2.0 (1.4–2.8)	< 0.001
35–54	1.6 (1.1–2.3)	0.01
≥ 55	1.0 (0.6–1.9)	0.9
Sex		
Female	1.0	
Male	1.6 (1.2–2.0)	< 0.001
STR to dust mite†		
No	1.0	
Yes	1.3 (1.0–1.8)	0.04
STR to silk		
No	1.0	
Yes	1.5 (1.1–2.2)	0.02

* Adjusting for age, sex, intensity of smoking, household correlations, and skin test reactivity to aeroallergens (dust mite, mixed tree pollen, mixed grass pollen, silk, artemisia, mold, tobacco leaf, and cockroach).

† *Dermatophagoides pteronyssinus* or *Dermatophagoides farinae*.

There is mounting epidemiologic evidence suggesting that allergic rhinitis is less common in rural China than in industrialized countries (9,11,30). Leung and colleagues (30) found a very low prevalence of “rhinitis ever” (3.7%) among children living in a rural area of southeast China (San Bu), in whom the prevalence of atopy (sensitization to one or more aeroallergens) was 49%. In our study of families of asthmatic subjects in Anqing, 46.9% of the participants were atopic. However, only 3.5% of the study subjects reported symptoms suggestive of allergic rhinitis.

Many studies conducted in industrialized countries with a Western lifestyle have shown an association between sensitization to perennial allergens and asthma (12–17). In a study of a birth cohort of New Zealand children followed to the age of 13 yr, sensitization to house dust mite, cat dander, and *Aspergillus fumigatus* were all independent predictors of asthma after adjustment for skin test reactivity to other allergens (OR for sensitization to dust mite = 6.7, 95% CI for OR = 1.2 to 13.4) (14). In a cross-sectional study of 4,295 subjects 6 to 24 yr of age living in the United States, sensitization to house dust and *Alternaria* were both independent predictors of asthma after adjustment for sensitization to other allergens and potential confounders (OR for sensitization to house dust = 2.0, 95% CI = 1.1 to 3.6; OR for sensitization to *Alternaria* = 2.8, 95% CI = 1.4 to 5.6) (16). Among children living in a desert environment in the United States, those sensitized to *Alternaria* at age 6 had 3.4 times higher odds of having asthma at ages 6 and 11 than nonreactors (17).

Leung and collaborators (30) conducted a cross-sectional study of the association between allergic diseases and skin test reactivity to five allergens (pollen, dust mite, mold, cockroach,

and animal dander) in Chinese children living in urban Hong Kong (n = 471) and in rural San Bu (n = 647). After adjustment for skin test reactivity to other allergens and potential confounders, sensitization to mold and animal dander were independent predictors of “wheeze or asthma ever” in Hong Kong (OR for sensitization to mold = 3.6, 95% CI = 1.8 to 7.2), but only sensitization to dust mite had a weakly significant association with “wheeze or asthma ever” in San Bu (OR = 5.6, 95% CI = 1.0 to 5.2) (30). Whereas sensitizations to mold and dust mite were independent predictors of rhinitis in Hong Kong, there was no significant association between sensitization to any of the allergens tested and rhinitis in San Bu (30).

Using a more stringent definition of asthma and examining skin test reactivity to 10 allergens, we found highly significant yet relatively modest associations between asthma and sensitization to dust mite and mold among families of asthmatic subjects in rural Anqing. Because Anqing is located along the northern bank of the Yangtze River and the annual average temperature is 15° C, the warm and humid subtropical climate likely provides a good habitat for dust mite and mold.

China is the homeland of silk. Allergy to silk can result from occupational exposure (sericulture), as well as after exposure to bed quilts or clothes filled with silk waste, particularly during the winter season (31, 32). In a study of 267 Japanese patients with allergic rhinitis, silkworm moth was the third most common sensitizing allergen, and a strong correlation was found between silkworm moth and silk (33). Although cases of silk-induced asthma have been reported in China (31), Japan (34), and Europe (35), ours is the first epidemiologic study in the English literature to examine the relationship between silk and either asthma or rhinitis.

We recognize several limitations to our study. First, our findings cannot be generalized to the entire population of Anqing. However, our study results apply to a group at risk for developing asthma (relatives of asthmatic subjects in Anqing). In addition, because the prevalence of asthma in the general population in Anqing is so low (19), a prohibitively large sample size would be needed to study the modest effects of exposure to aeroallergens on asthma in this population. Second, this is a cross-sectional study, and one cannot conclude that allergen sensitization preceded either asthma or rhinitis. Third, nondifferential misclassification of the diagnosis of allergic rhinitis may have occurred, as our definition was based solely on the presence of nasal symptoms. Nonetheless, we found a linear relationship between the number of positive skin tests to allergen and rhinitis, as well as a positive association between asthma and rhinitis in our study population. Fourth, we did not examine skin reactivity to cat or dog allergens. However, pet ownership is exceedingly rare in Anqing (X. Xu, personal communication).

In conclusion, sensitization to perennial aeroallergens (dust mite and mold) is predictive of asthma in families of asthmatic subjects in a rural province of China. Physical measures to reduce dust mite allergen levels may result in improvement of respiratory symptoms in mite-sensitized persons with asthma and/or allergic rhinitis in China. Sensitization to silk, a seasonal aeroallergen, was the strongest predictor of rhinitis in our study population. Avoidance of exposure to silk may result in symptomatic improvement in sensitized persons with allergic rhinitis in China and in other oriental countries. Our findings also suggest that allergic rhinitis is far less common among asthmatic subjects in rural China than in asthmatic subjects in industrialized countries with a Western lifestyle. The presence or absence of yet unexplored genetic and/or environmental factors may prevent the development of allergic rhinitis in asthmatic subjects living in rural China.

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