

Sensitization to Silk and Childhood Asthma in Rural China

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ABSTRACT. *Objective.* Sensitization to perennial aeroallergens is associated with asthma in industrialized countries with a Western lifestyle. Because silk products are commonly used in Chinese society, we were interested in examining the relation between sensitization to silk and asthma.

Design. Cross-sectional study of 871 children in 503 families living in Anqing, a predominantly rural province of China.

Results. After adjustment for age, gender, familial correlations, and sensitization to other aeroallergens, skin test reactivity to silk was an independent predictor of asthma (odds ratio = 2.6; 95% confidence interval = 1.2–5.7). This association became stronger after inclusion of the eosinophil count and history of parasitic diseases of the participants in the multivariate model (odds ratio = 3.6; 95% confidence interval = 1.4–8.9).

Conclusion. Because sericulture is an important activity in China and other countries throughout the world, sensitization to silk may influence the pathogenesis and severity of asthma in people living in these nations. *Pediatrics* 2001;107(5). URL: <http://www.pediatrics.org/cgi/content/full/107/5/e80>; asthma, sensitization to silk, rural China.

ABBREVIATIONS. OR, odds ratio; CI, confidence interval.

The silk production industry began in China ~2640 BC, when the Empress Hsi-ling Shih is credited with learning how to raise silkworms and unwind the silk filaments from their cocoons. Although sericulture then spread to Japan and later westward over India and Central Asia, China is the main producer of raw silk in the world today.

Skin test reactivity to perennial aeroallergens, such as the house dust mite, animal dander, and mold, is strongly associated with asthma in countries with a Western lifestyle.^{1–6} Because silk is an aeroallergen that is ubiquitous in Chinese society,⁷ we were interested in examining the relation between sensitization to silk and asthma among 871 children living in Anqing, a predominantly rural province of China.

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Received for publication Nov 7, 2000; accepted Dec 21, 2000.

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METHODS

Anqing stretches for ~80 km along the northern bank of the Yangtze river. The annual temperature is 15°C. Anqing has 3 urban areas and 8 rural counties, with a total area of 15 000 km.² The population in 1990 was 5.8 million (urban, 9%; rural, 91%). Families were selected from the general population. All families were selected by a 2-stage random sampling technique using 1992 census records. The sample unit at the first stage was the administrative unit (eg, the village). At the second stage, the unit was the household. The following criteria were used for inclusion of families in the study: 1) 2 or more siblings in the family; 2) age of the youngest sibling ≥6 years; and 3) both parents available.

Procedures

Informed consent was obtained from the parents of all participating children <12 years old and from all participating children >12 years old. 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.

The following procedures were conducted: 1) completion of a modified American Thoracic Society Division of Lung Diseases questionnaire including questions on respiratory symptoms, respiratory health status, occupational history, tobacco use, home environment, family history of asthma and other chronic diseases, and current status and history of parasitic diseases; 2) skin testing of reactivity to 10 allergens along with a positive and a negative control; 3) collection of blood samples for measurement of eosinophil count; and 4) examination of a single stool specimen for ova and parasites. The study was approved by the institutional review boards of the Brigham and Women's Hospital, the Anhui Medical University Center for Ecogenetics and Disease Control, and the Harvard School of Public Health.

Peripheral Blood Eosinophil Count

Eosinophil count in peripheral blood, henceforth referred to as eosinophil count, was measured by Coulter-counter techniques at the Hematology Laboratory of Anhui Medical University. Because the values obtained did not follow a normal distribution, they were transformed to a log₁₀ scale for analysis.

Allergy Skin Testing

Skin testing was performed with a slightly modified version of the semiquantitative puncture method developed by Santilli et al.⁸ 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*, *Dermatophagoides farinae*, *Artemisia vulgaris*, and mulberry silk waste (henceforth referred to as silk). The silk, *A. vulgaris*, polyvalent molds, and house dust antigens were provided by the Department of Allergy of Peking Union Medical College (Beijing, China); the remaining antigens were purchased from Bayer Corp (Spokane, WA). The preparation of the silk antigen has been described elsewhere.⁷ A test was considered positive if the diameter of the skin wheal was ≥3 mm after subtracting the negative control.

Stool Examination for Ova and Parasites

Microscopic examination of wet mounts of stool specimens for ova and parasites was performed at the Parasitology Laboratory of Anhui Medical University Center.

Definition of Asthma

Our definition of asthma was based on affirmative answers to the questions "Do you have asthma?" and "Has your asthma been confirmed by a doctor?" as well as a history of either ≥ 1 respiratory symptoms (cough, wheezing, or nocturnal cough/wheezing) or asthma attacks in the preceding 12 months.

Definition of Other Predictor Variables

Age, a potential confounder of the relationship between sensitization to allergens and asthma, was treated as a continuous variable. There was no reporting of current smoking in any of the participating children, and they were all presumed to be non-smokers for study purposes.

Statistical Methods

Bivariate relationships between predictor and outcome variables were analyzed by χ^2 or Fisher's exact tests in the case of pairs of categorical variables or 2-tailed *t* tests in the case of a categorical and a continuous variable. To account for correlations among individuals from the same household, methods developed by Zeger and Liang⁹ with generalized estimating equations for the logistic case were used to evaluate the relationship between the dependent and independent variables. All of the analyses were performed with the SAS statistical software package (SAS Institute, Inc, Cary, NC).

RESULTS

Participant Characteristics

The study originally included 923 participants ≤ 14 years in 539 families in Anqing, China. The present analyses were limited to the 871 children who had complete information on peripheral blood eosinophil count and skin test reactivity to aeroallergens. No statistically significant differences in age; gender; physician-diagnosed asthma; wheezing, cough, or nocturnal symptoms in the preceding 12 months; skin test reactivity to ≥ 1 aeroallergen; or peripheral blood eosinophil count were found between participants included in the analysis ($n = 871$) and those excluded ($n = 52$).

The characteristics of the 871 participating children are summarized in Table 1. The mean and standard deviation of the age of the 871 study participants were 10.6 ± 2 years; the age range of these participants was 6 to 14 years. The geometric mean eosinophil count of the study participants was $146/\text{mm}^3$. Information on history of past parasitic diseases and results of a single stool examination for ova and parasites were available for 677 of the 871 study

participants (77.7%). Ninety of these 677 participants (13.3%) had a history of parasitic diseases ($n = 55$) and/or a positive examination for ova and parasites ($n = 54$).

Predictors of Asthma on Univariate Analysis

No statistically significant difference was found between the mean ages of asthmatic and nonasthmatic children (10.1 ± 2.2 years vs 10.6 ± 2.0 years; $P = .14$). There was a statistically significant association between skin test reactivity to silk and asthma (Table 2). However, sensitization to any of the other 9 aeroallergens examined was not significantly associated with asthma ($P > .2$ in all cases).

Participants whose eosinophil count was in the upper 2 quartiles of the $\log_{10}$ distribution of eosinophil count had significantly higher odds of having asthma than did those in the bottom quartile (Table 2).

Asthma and Sensitization to Silk

Table 3 summarizes the results of multivariate analyses of the relation between asthma and skin test reactivity to aeroallergens. After adjustment for age, gender, familial correlations, and skin test reactivity to other aeroallergens using generalized estimating equations, children who were sensitized to silk had 2.6 times higher odds of having asthma than did nonreactors (model 1). This association between sensitization to silk and asthma became stronger and of greater statistical significance after inclusion of the eosinophil count of the participants in the multivariate model, as either a categorical variable (model 2) or a linear term (model 3).

DISCUSSION

To our knowledge, this is the first population-based study to demonstrate an association between sensitization to silk and childhood asthma. After adjustment for age, gender, familial correlations, and sensitization to other aeroallergens, skin test reactivity to silk was an independent predictor of asthma among 871 children living in rural China (odds ratio [OR] = 2.6; 95% confidence interval [CI] = 1.2–5.7).

In a study of 737 children living in San Bu, a rural province of southeast China, Leung and collaborators¹⁰ found no association between sensitization to any of 4 aeroallergens (pollen, cockroach, mold, and animal dander) and asthma. Although sensitization to house dust mite was associated with asthma, this association was of borderline statistical significance (OR = 5.6; 95% CI = 1.0–30.2). Skin testing to silk was not performed in this study.

Matsumura and colleagues¹¹ reported 4 cases of childhood asthma attributable to silk inhalation. In 2 of their study participants, provocative tests with inhalation of silk extract resulted in strong asthmatic attacks. Chaoming and collaborators⁷ reported 64 cases of silk-induced asthma among children ≤ 15 years of age who were evaluated at an allergy clinic in Beijing. The diagnosis of asthma related to silk exposure was based on history, skin prick testing, and conjunctival or nasal provocation testing with silk extract. Of the 64 children included in this series,

TABLE 1. Characteristics of 871 Study Participants in Anqing, China

Participant Characteristics	<i>n</i> (%) [*]
Gender	
Female	390 (44.8)
Male	481 (55.2)
Physician-diagnosed asthma	81 (9.4)
Wheezing in preceding 12 mo	55 (6.3)
Cough in preceding 12 mo	54 (7.3)
Nocturnal cough or wheezing in preceding 12 mo	14 (1.7)
Asthma†	34 (3.9)
Skin test reactivity to ≥ 1 aeroallergen	404 (46.4)
Peripheral blood eosinophil count $\geq 250/\text{mm}^3$	294 (33.7)

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

[†] Physician-diagnosed asthma and history of either respiratory symptoms or asthma attacks in the preceding 12 months.

TABLE 2. Predictors of Asthma on Univariate Analysis

Predictor	Asthma n (%) [*]	OR (95% CI)	P Value
Gender			
Female	13 (3.4)	1.0	
Male	21 (4.4)	1.3 (0.7–2.7)	.42
STR to silk			
No	28 (3.5)	1.0	
Yes	6 (8.5)	2.5 (1.0–6.3)	.04
STR to house dust mite†			
No	21 (3.7)	1.0	
Yes	13 (4.4)	1.2 (0.6–2.4)	.59
STR to <i>A vulgaris</i>			
No	32 (3.8)	1.0	
Yes	2 (6.9)	1.9 (0.4–8.1)	.32
STR to mold			
No	32 (3.8)	1.0	
Yes	2 (7.4)	2.0 (0.5–8.9)	.29
Eosinophil count (quartiles of logarithmic distribution)			
20–49/mm ³	1 (0.6)	1.0	
50–119/mm ³	4 (2.1)	2.6 (0.3–21.9)	.39
120–269/mm ³	15 (6.5)	9.3 (1.5–58.9)	.02
270–3620/mm ³	14 (4.9)	6.8 (1.1–43.3)	.04

STR indicates skin test reactivity.

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

† *D pteronyssinus* or *D farinae*.

TABLE 3. Multivariate Analysis of the Relation Between Skin Test Reactivity to Aeroallergens and Asthma

	OR (95% CI), P Value		
	Model 1 [*]	Model 2†	Model 3‡
Skin test reactivity to silk			
No	1.0	1.0	1.0
Yes	2.6 (1.2–5.7) .02	3.6 (1.4–8.9) <.01	3.4 (1.4–8.5) <.01

^{*} Adjusting for age; gender; familial correlations; and skin test reactivity to house dust mite (*D pteronyssinus* or *D farinae*), mold, cockroach, mixed tree pollen, mixed grass pollen, *A vulgaris*, and tobacco leaf.

† Adjusting for eosinophil count (as quartiles of logarithmic distribution) and current and past parasitic diseases (by history or stool examination) in addition to all of the variables included in model 1.

‡ Adjusting for eosinophil count (as a continuous variable on the logarithmic scale) and current and past parasitic diseases (by history or stool examination) in addition to all of the variables included in model 1.

60 (93.7%) were classified as having moderate to severe asthma. Johansson and colleagues¹² reported a series of 50 patients diagnosed with asthma caused by allergy to bed quilts filled with silk waste at the Department of Dermatology and Allergy at the University Hospital in Zurich. On an average, the first symptoms appeared 7 months after exposure to silk. The study participants were 10 to 58 years old, and 49 of the 50 patients (98%) improved with avoidance of exposure to silk. Sensitization to silk and occupational asthma have long been known to be hazards of sericulture.^{13–15}

China is the homeland of silk. The allergenicities of the 2 groups of silk used in China, mulberry and wild, are very similar.¹² However, allergy to mulberry silk is more frequent in China than is allergy to wild silk because mulberry silk is more commonly used.⁷ Silk is obtained from the cocoon of the silkworm.^{14,15} Each cocoon consists of a single thread secreted by the worm. Because the emerging moth would break the thread, the pupae are killed by steaming the cocoons. The steamed cocoons are boiled, and then the threads are rolled over reels.

Each thread is a double filament of protein material (fibroin) glued together with sericin, an allergenic gummy substance that is extracted during processing of the silk threads.^{14,15} The final textile products of silk, however, are most often nonallergenic.⁷ Sensitization to mulberry silk can be attributable to allergens in the silk cocoon, silkworm pupae, and unprocessed silk threads. Silk workers involved in sorting or boiling the cocoons and in reeling, rearranging, or degumming the threads can be sensitized to silk by inhalation of airborne allergens.^{14,15} Unprocessed silk threads that are broken during reeling (silk waste) are used by the Chinese to fill bed quilts, clothes, toys, and mattresses.⁷ Children can also be exposed to silk if their parents work in sericulture.⁷ Although exposure to silk waste may be more intense during the winter months, when children often use blankets filled with this material, perennial exposure to silk waste is likely to occur in some children. Given the pervasive presence of silk products in Chinese culture, avoidance of exposure to silk waste may be difficult unless its use is greatly reduced.

Peripheral blood eosinophilia is associated with asthma and increased airway responsiveness in Western countries with low prevalence of parasitic diseases.^{16,17} The role of peripheral blood eosinophil count as a marker of asthma in the Far East, however, has not been adequately studied. Our findings suggest that the eosinophil count in peripheral blood may be a useful marker of asthma in areas of the Far East with a low to moderate prevalence of parasitic illnesses.

We recognize several limitations to our findings. First, this is a cross-sectional study, and a temporal relationship between sensitization to silk and the development of asthma, thus, cannot be demonstrated. Second, our definition of asthma was based on responses to a standardized questionnaire, because we did not measure airway responsiveness to bronchoconstrictors in the study participants. However, our definition of asthma has been found to be adequate for use in population-based studies. Third, we examined only a single stool specimen for ova and parasites. Significant underestimation of the true prevalence of parasitic disease in Anqing is unlikely, however, because the geometric mean eosinophil level in our study population is far lower than that of heavily parasitized groups.¹⁷ Fourth, we did not examine skin test reactivity to cat or dog allergens. However, ownership of these pets is exceedingly rare among people living in Anqing. Fifth, because the prevalence of childhood asthma in Anqing is low (3.9%), our statistical power may not have been adequate to detect a modest association between any of the aeroallergens examined and asthma.

CONCLUSION

Sensitization to silk is an independent predictor of childhood asthma in rural China. Because sericulture is a very important activity in China and other countries (eg, India and Japan), sensitization to silk may influence the pathogenesis and severity of asthma in children living in these nations. Additional research is needed to examine whether sensitization to silk in early life precedes the development of asthma among children living in silk-producing nations and to assess whether avoidance of exposure to silk products (eg, silk waste) results in symptomatic improvement of silk-induced asthma.

ACKNOWLEDGMENTS

This study was supported in part by Grant AI56371 from the National Institutes of Health and by Millennium Research.

Dr Celedón is supported by a Charles A. King Trust Fellowship

Award. Dr Palmer is a Winston Churchill Memorial Trust Fellow and an Australian-American Educational Foundation Fulbright Fellow.

We thank the study participants; the staffs of Anhui Medical University and the Anqing Health Bureau; Jaylyn Olivo for her editorial assistance; and Dr Frank E. Speizer for his helpful comments on the manuscript.

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