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Risk Factors for Development of Asthma in Thai Adults in Phitsanulok: A University-based Study

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SUMMARY Studies have shown that asthma in children is caused by environmental and genetic factors. In adult asthma, risk factors were less well recognized. Likewise, in Thailand, data in adult asthma is limited. This study aimed to evaluate risk factors, determine skin reactivities to allergens, and assess concomitant allergy among adult asthma in Phitsanulok, a major city in the lower northern Thailand. Five hundred and thirteen Naresuan University staff members and students completed 2 sets of questionnaires and underwent allergy skin prick tests. The first set of questionnaires was standardized Thai version of ISAAC questionnaire for identifying asthma, allergic rhinitis, and atopic eczema. The second set was modified from ISAAC phase II questionnaire to identify asthma risk factors. Fifty-eight subjects (11.6%) were identified as having physician's diagnosed asthma and 89 subjects (17.7%) wheezed in the past 12 months. Among 89 subjects, 14.4% wheezed more than once a month, 45.6% had wheezes interfering with sleep. Concomitant allergic rhinitis, rhinoconjunctivitis and atopic eczema among these asthma subjects were 82.5%, 67.9%, and 14.9%, respectively. Eighty seven point nine percent of asthmatic subjects had positive skin reactivities to at least one allergen. Two of the most common allergens were house dust mites and cockroaches. Maternal smoking during pregnancy, smoking among family members, and family history of allergy were statistically significant risks for developing asthma, while having a rice field around the residence represented a significant protective factor. In conclusion, high prevalence of asthma presented in Phitsanulok and many asthmatic subjects were partly controlled or uncontrolled. The environment such as a rice field could protect against asthma, however atopy and smoking exposure were significant risks for asthma development

Allergic diseases have increased worldwide including in Thai adult population. The study in 2003 showed prevalence of adult asthma was 12.1%[1] which increased from 2.4% in 1975, 4.8% in 1995 and to 10.1% in 1998.[2-4] These reports, however, were carried out in different regions of Thailand. Factors that influence the asthma risk causing the development and expression of asthma include host and environmental factors of which mechanism are complex and interactive.[5,6] The host factors are primarily genetic, while environmental factors are allergens, infections (predominantly virus), occupational sensitizers, tobacco smoke, outdoor/indoor air pollution and diet.[5,6] Much of what is known about asthma risk factors comes from studies among young children. Risk factors for the development of asthma in adults, particularly *de novo*, among adults who did not have asthma in childhood, are less well defined.[6] In Thai adult asthma, the study of risk factors is also limited compared to asthma in childhood. Among

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Thai allergic children, most surveys showed that two of the most common allergens were house dust mites and cockroaches.[7,8] There are a few data reporting aeroallergen sensitization among Thai adult asthma. A study in 1997 among both Thai children and adult with allergic rhinitis showed skin reactivities to *Dermatophagoides pteronissinus* (Dp), *D. farinae* (Df), cockroaches of 76%, 79%, and 60%, respectively.[9] Two studies in Bangkok and Chiang Mai, the upper northern Thailand showed the two most common sensitizing allergens in adult asthma to be house dust mites[10, 11] and cockroaches[11] with the sensitizing rate ranging from 27 to 41% and 15.5%, respectively. Skin reactivity to storage mite (Blo t 5) was also found 13.3% in atopic adult.[10] The objectives of this study are 1) to evaluate risk factors, 2) to determine skin reactivity to allergens, and 3) to evaluate concomitant allergy among adult asthma in Phitsanulok, a major city in the lower northern Thailand.

MATERIAL AND METHODS

Five hundred and thirteen staff members and students of Naresuan University in Phitsanulok were included in the 2004 study. All subjects completed two sets of self-reported written questionnaire and underwent skin prick tests for allergen sensitization. Asthmatic subjects were identified by the first set of written questionnaires which was a standard questionnaire developed by the International Study of Asthma and Allergies in Childhood (ISAAC). This questionnaires were translated into Thai and was utilized by ISAAC study for both Thai children[12,13] and adults[1,2] for evaluating prevalence of asthma, allergic rhinitis and atopic eczema. From the questionnaire, asthma was determined by physician's diagnosed asthma; allergic rhinitis was limited to physician's diagnosed hay fever (corresponding to the Thai term of 'allergic to air'). Allergic rhinoconjunc-tivitis was collected from positive responses to runny nose, rhinorrhea, stuffy nose without a cold, in addition to itchy eyes. Atopic eczema was estimated from those with allergic rashes at the flexural areas. The second set of questionnaires included the questions about risk factors for asthma which were modified from a risk factor questionnaire of ISAAC-phase two.[14] These questions included birth history, family history, environment, smoke exposure, illnesses, antibiotic use, vaccination, exercise and diets. Birth history included birth weight and maternal smoking during pregnancy. Questions on environmental exposure included pet exposure, bedroom environment, and existing structures within 100 meters around a subject's residence. The answers for the last environment question comprised an industrial factory, a street, an orchard, a garden, a grass field, a zoo, a rice field, a construction area, and others. Pertussis, tuberculosis, and migraine headache were among questions regarding concomitant illness. Allergy skin prick tests were performed with a standard panel of 15 standardized allergen extracts (Greer Laboratories, NC, USA). These included *Dermatophagoides pteronissinus* (Dp) 10,000 AU/ml, *D. farinae* (Df) 10,000 AU/ml, American cockroach 1:20 w/v, cat 10,000 BAU/ml, dog 1:20 w/v, Bermuda grass 10,000 BAU/ml, Johnson grass 1:20 w/v, *careless weed* 1:40 w/v, *acacia* spp. 1:40 w/v, *Alternaria tenuis* 1:20 w/v, *Cladosporium herbarum* 1:40 w/v, *Penicillium* mix 1:20 w/v, *Aspergillus* mix 1:20 w/v, egg white 1:20 w/v, cow's milk 1:20 w/v, peanut 1:20 w/v, shrimp 1:20 w/v, and fish mix 1:20. Negative control was 50% glycerine and positive control was 10 mg/ml histamine dihydrochloride. A skin test was regarded as positive if a wheal size (means of the 2 longest orthogonal dimensions) was at least 3 mm in diameter larger than negative control. The frequency of asthma-related symptoms and skin test reactivities were analyzed by a STATA program. To compare concomitant allergic rhinitis, allergic rhinoconjunctivitis, atopic eczema in asthmatic and non-asthmatic subjects, a Chi-square analysis with Yates correction was used. Risk factors for asthma from the questionnaires were analyzed by multiple logistic regression analysis.

This study was reviewed and approved by the human rights and ethic committee of Naresuan University. Informed consent was obtained before study participation.

RESULTS

Among 513 subjects, there were 153 males (29.8%) and 360 females (70.2%) with a male to female ratio of 1:2.4. The mean age was 24 years with the age range of 17-60 years. Eighty four percent of patients were between 17 and 30 years. Fifty-eight subjects (11.6%) had physician's diagnosed asthma and 89 subjects (17.3%) wheezed in the past 12 months (Table 1). In asthmatic subjects, there were

21 males and 37 females with a male to female ratio of 1:1.8. Among subjects who wheezed in the past 12 months, 40% had at least 4 wheezing attacks in the past year and 14.4% wheezed more than once a month. In addition, wheeze affecting sleep was presented in 45.6% with 21.1% having night-time wheeze at least once a week and severe wheeze interfering with speech occurred in 24.5% (Table 2). Exercise-induced wheeze was reported in 16.3%. Allergic rhinitis and rhinoconjunctivitis were identified in 47 and 41.8 %, respectively. Forty-four point three percent reported symptoms affecting normal activities. Eighty-two point five percent of asthmatic subjects had allergic rhinitis compared to 49.2% of non-asthmatic subjects (OR = 4.9, CI 2.4-9.9, $p < 0.001$). Asthma was presented in patient with allergic rhinitis 4 times more than those without allergic rhinitis (18.4%, 4.4 %). Likewise in patients with allergic rhinoconjunctivitis, asthma was presented more than those without allergic rhinoconjunctivitis (19.1% and 6.4%). Conversely asthmatics had more rhinoconjuncitvitis symptoms than those without asthma (67.9%, 38.1%). These differences were statistically significant, as shown in Table 3. Atopic eczema was presented among asthmatic subjects more often than those without asthma (14.9% and 10.8%). However the difference was not statistically significant (p = 0.25).

Among risk factors, 51 of 58 asthmatics (87.9%) had at least one positive skin test to allergen compared to 71.3% in non-asthmatic subjects (OR = 2.9, CI 1.3 - 6.6, p = 0.007). The percentage of positive skin reactivities in asthmatics to Dp, Df, American cockroach, cat, shrimp, Johnson grass, Bermuda grass, careless weed, acacia, dog, peanut, *Aspergillus*, *Alternaria*, *Cladosporium*, *Penicillium* were 81, 77.2, 75.9, 45.6, 44.4, 41.4, 38.6, 34.5, 34.5, 27.6, 19.6, 19.0, 13.8, 10.3, 5.2%, respectively (Fig. 1). The study on other predisposing factors showed that maternal smoking during pregnancy, family-member smoking and family history of allergy were statistically significant risks for developing asthma (adjusted OR = 3.6, CI 1.6 - 8.3, p = 0.002; adjusted OR = 2.2, CI 1.2 - 3.9, p = 0.008; adjusted OR = 2.0, CI 1.1 - 3.8, p = 0.029, respectively). Interestingly, having a rice field close to residences was identified as a

Table 1 Prevalence of allergy-related symptoms (N = 513).

Allergy-related symptoms	Positive response (%)
Diagnosed hay fever/ allergic rhinitis	47.0
Rhinitis together with eye symptoms	41.8
Wheeze within the past 12 months	17.3
Diagnosed asthma	11.6
Atopic eczema	20.3

Table 2 Asthma severity among subjects who wheezed in the past 12 months (N = 89)

Severity related symptoms	Positive response (%)
Wheeze affecting sleep	45.6
Wheeze affecting sleep ≥1/ week	21.1
Severe wheeze interfering with speech	24.5
Wheezing attack >1/ month	14.4

Table 3 Percentage of asthma with concomitant rhinitis or rhinoconjunctivitis

	Positive response (%)	OR	95% CI
Allergic rhinitis with asthma	18.4	4.9	2.4-9.9
Rhinoconjunctivitis with asthma	19.1	3.4	1.9-6.2
Asthma with allergic rhinitis	82.5	4.9	2.4-9.9
Asthma with rhinoconjunctivitis	67.9	3.4	1.9-6.2

OR; odds ratio, 95%CI; 95% confidence interval

significant protective factor (adjusted OR = 0.35, p = 0.002) (Table 4). Neither having pet nor animal in the house nor antibiotic exposure was significant risk for developing to asthma. Moreover, other risk factors such as birth weight, vaccination, exercise, illnesses and diet did not significantly affect the development of asthma.

DISCUSSION

This is an extension study from our previous epidemiologic survey on adult allergy in Phitsanulok, a major city in the lower northern Thailand.[1] Prevalence of diagnosed asthma and wheeze among adults in the past 12 months were 9.8 and 12.1%, the figures were surprisingly higher than corresponding figures from those in Bangkok (8.8% and 10.1% respectively).[2] Therefore, we conducted a study on risk factors for developing asthma in these population. The high prevalence of allergic diseases among our population could be due to the fact that our populations were not random and included volunteers which were biased to have positive responses to questionnaire and high positive skin tests. Among subjects who wheezed in the past 12 months, half had wheezed affecting their sleep with 21.1% had symptom at least once a week. Twenty-four point five percent had severe attack and 14.4% wheezed more than once a month. These figures demonstrated that symptoms among a large number of asthmatic subjects were uncontrolled or partly controlled and their severity were in the class of mild to moderate persistent. This suggested that inhaled corticosteroid may be under used. As for concomitant allergy, allergic rhinitis and rhinoconjunctivitis were risk factors for asthma which was similar to previous studies in adults[1,2] and in the recent phase III ISAAC study.[15] There was a 1.7-1.8 folds increase of allergic

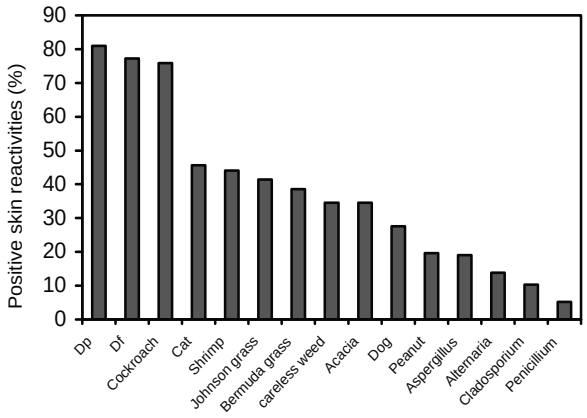

Fig. 1 Percentage of allergen sensitization in adult asthma. Dp and Df represented *Dermatophagoides pteronissinus* and *Dermatophagoides farinae*, respectively.

Table 4 Risk factors for developing asthma

Risk factors	Adjusted odd ratio	95% CI	*p* value
Maternal smoking during pregnancy	3.6	1.6-8.3	0.002
Family member smoking	2.2	1.2-3.9	0.008
Family history of allergy	2	1.1-3.8	0.029
A residence surrounded by a rice field	0.35	0.18-0.67	0.002

rhinitis and rhinoconjunctivitis among asthmatic subjects compared to those without asthma. These data confirmed the notion of 'the united airway'[16,17] that asthma and allergic rhinitis usually co-exist.

Genetic predisposition has been shown to be a major factor influencing the development and expression of asthma. Current data indicated that multiple genes may be involved in the pathogenesis of asthma.[18,19] For example a gene (or genes) governing bronchial hyperresponsiveness is located near a major locus that regulates serum IgE levels on chromosome 5q.[20] Our study has shown that family history of allergy was also a significant risk in which reinforces the genetic predisposition. House dust mites and cockroaches remained two of the most common sensitized allergens in our adult asthma as in Thai asthmatic children[8, 21] and in allergic adults,[9-11] although higher cockroach sensitization in our adult asthma was observed. Many previous works in children have demonstrated that sensitization to house dust mite, cat dander, dog dander[22, 23] and *Aspergillus* mold[24] were independent risk factors for asthma-like symptoms in children up to 3 years of age. The prevalence of sensitization to house dust mites and cockroaches appears to be directly correlated with exposure.[22, 25] Therefore, a significant higher percentage of allergen sensitizations in our adult asthma indicated that atopy plus allergen exposures are important risks which emphasized both genetic and substantial environmental factors. Adults in Phitsanulok who had genetic predisposition to atopy and persistently exposed to high antigen concentration of house dust mite or cockroach in the environment, could subsequently become asthmatic. A much higher sensitization in this study compared to another adult study[11] (87.9%, 43.7% respectively) was likely from enrollment of more allergic subjects as mentioned above. Cockroach and cat dander sensitization in Phitsanulok were surprisingly high compared to Bangkok.[8, 9, 11] Moreover, skin reactivities to grass pollens, careless weed and acacia were considerably high. These data may exhibit geographic difference in atopy as well as environment, and may demonstrate that pollens and outdoor allergens could be more influential on adult asthma in Phitsanulok than in Bangkok. Further studies on the amount of indoor and outdoor allergens in Phitsanulok are required to confirm these findings.

Tobacco smoke is associated with accelerated decline of lung function in people with asthma and could increase asthma severity.[26, 27] Studies of lung function immediately after birth have shown that maternal smoking during pregnancy has an influence on lung development.[28] Our study affirmed the influence of tobacco smoke on asthma to be significant risk such as from maternal smoking during pregnancy and the smoking among family members. Either of these two mechanisms of tobacco smoke causing the development of asthma in Thai adult may need to be clarified.

Factors influencing the development of asthma reported in current data such as illnesses, pets in the house, vaccine and diet did not appear to be significant risks in our survey. We recognized that having a rice field around the residence was a protective factor in our adult asthmatic subjects. The possible explanations on this result could be related to hygiene hypothesis and less pollution exposure. Increased air pollution has been shown to cause asthma exacerbation whereas its role in the development of asthma is less well defined.[6] In hygiene hypothesis, it was observed that high levels of endotoxin in the farm with livestocks could protect against allergic diseases.[29] While the endotoxin level has not been explored in Thailand, people who live in the rice field are farmers and are likely to have their own farms and livestocks; therefore there may be high level of endotoxin in a rice-field environment. Whether the effect of endotoxin in relation to hygiene hypothesis is applicable to Thai people and Thai environment remains to be further investigated.

In summary, this survey exhibited that a large amount of adult asthma in Phitsanulok was partly controlled or uncontrolled, and was mild to moderate persistent in severity. The risk factors for development of asthma included smoking among pregnant mother and family members, alllergen sensitization, and atopy in the family whereas rice field is associated with less asthma. Further studies need to be performed on the levels of both allergen and endotoxin in Thai rural as well as urban areas.

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