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Development of a Nomogram for Identification of Asthma among Adults in Epidemiologic Studies

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Introduction

Asthma is a serious health problem with increased prevalence and incidence over recent decades in both children and adults. Identification of study subjects likely to have asthma is a key step in asthma investigations. Epidemiologic investigations have utilized questionnaires to determine asthma prevalence.¹⁻⁶ Currently there is no universally accepted standard definition of asthma for case identification in adult studies of asthma. It is essential to develop predictive models to identify asthma among adult populations.

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The clinical diagnosis of asthma in adults is made based on the presence of asthma related symptoms in combination with documentation of reversible airway obstruction. In epidemiologic studies of children and adults, questionnaires are frequently used to collect information on the presence of wheezing, medication use for asthma, shortness of breath, cough and chest tightness, in order to identify persons with asthma. Much work has been done on validating such questionnaires in pediatric populations, such as the International Study of Asthma and Allergies in Childhood (ISAAC),⁷⁻¹⁰ and in adult populations, such as the European Community Respiratory Health Survey (ECRHS),¹¹ among others. Use of questionnaires is a convenient and cost-efficient means of identifying asthma in large populations. However, there are recognized limitations of determining asthma based on a single question on surveys.¹² In addition, there are more diseases in adult populations that overlap with asthma than in pediatric populations, thus objective measurements of airway responsiveness, together with the presence of asthma related symptoms, have been used to increase the accuracy of asthma case identification in epidemiological studies of adult asthma, such as Shanghai Women's Asthma and Allergy Study (SWAAS) and others.^{11,13}

Methacholine challenge testing (MCT) and/or test of reversibility to short-acting beta-agonists are objective measurements used to assess bronchial hyperresponsiveness. However, there are practical limitations to performing this testing since it is costly, labor-intensive and time-consuming, and there can be variability in results secondary to environmental and treatment factors.¹⁴ Because of the expense, difficulty associated with this physiological testing, and questions regarding whether MCT should even represent a gold standard, questionnaires remain the principal instrument used to identify asthma in large population based epidemiologic studies.

While most previous published studies have focused on the association of individual asthma related variables with the occurrence of asthma in adults, Pekkanen and colleagues have suggested that the sum of positive answers to asthma symptom questions as a continuous score is better than individual symptoms for studying the etiology of asthma.¹⁵ The objective of the present study was to develop a scoring system to serve as an efficient evaluation tool for asthma case identification for use in large population-based studies of adult asthma by providing an individual probability of asthma using a combination of predictor variables that are readily collected via questionnaire. Survey variables were weighted depending on their predictive value and to avoid the use of laboratory testing of bronchial hyperresponsiveness.

Methods

From among over 65,000 women enrolled in the Shanghai Women's Asthma and Allergy Study (SWAAS), a prospective incidence study ongoing in Shanghai, China, the first 268 women who completed both the questionnaire survey and pulmonary function testing were included in the present study. The objectives and design of the SWAAS have been described in detail elsewhere.¹³ Figure 1 is a flow diagram of the parent study cohort and the included study population entry criteria. Briefly, 65,372 women aged 40-69 years from seven urban districts of Shanghai were recruited to participate in the initial asthma screening survey with an overall participation rate of 91% between 2003 and 2007. Information on respiratory signs and symptoms, medication use, self-reported ever asthma, physician-diagnosed asthma, personal history of allergic rhinitis and eczema, and family history of asthma or allergy, has been obtained using the validated structured ISAAC questionnaire administered by trained interviewers from Shanghai Cancer Institute through an in-person home interview.¹³ Study subjects were referred for MCT or test of reversibility at Zhongshan Hospital, Fudan University to confirm the diagnosis of asthma if the subject had any signs and symptoms of asthma after baseline survey. Individuals with signs and symptoms of asthma ($n = 377$) were invited to undergo MCT or test of reversibility to short-acting β agonists at Zhongshan Hospital, Fudan

University to confirm the diagnosis of asthma. Ninety-four patients refused testing. Five subjects did not undergo MCT because of contraindications. Lung function testing was performed on 278 women.

Standard ATS/European Respiratory Society protocol was employed for MCT. In addition, all PFT were read by both trained pulmonologists at the Pulmonary Function Laboratory at ZhongShan Hospital, as well as an independent PFT oversight committee. Final determination of any discrepant cases was determined by the PFT oversight committee, or retesting of the subject. Spirometry was performed according to the Body Temperature and Pressure Standard (BTPS) convention with a spirometer (Jaeger, Germany and the ASTOGRAPH tcr-6000M, Chest Corporation, Japan) which was calibrated and maintained to acceptable respiratory function laboratory standards.¹⁶ Prior to spirometric testing, subjects were asked to withhold bronchodilator medications, and those medications which interfere with methacholine. The following parameters were measured: forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), forced expiratory flow at 25–75% (FEF₂₅₋₇₅), peak expiratory flow rate, and flow volume loops. The above parameters were measured three times consecutively and FEV₁ values had to be within 5% to be considered valid. For the analysis, the parameters from the test associated with the highest FEV₁ were used.

MCT was performed if baseline FEV₁ was $\geq 70\%$ of predicted. Two-fold incremental concentrations of methacholine chloride (Tokyo Chemical Industry Co. Ltd, Tokyo Kasei, Japan) reconstituted with physiological saline were prepared from 0.015 to 0.96 mg/ml. Methacholine was inhaled with a synchronized nebulizer/dosimeter (Methapharm Inc. FL). Five breaths at each dose up to 0.96 mg/ml (maximal dose) were used with 0.6 second pulse duration. Spirometry was repeated 3 minutes after each dose of methacholine. A positive test was defined as a 20% fall from baseline FEV₁. Following testing, subjects received salbutamol, and spirometry was repeated to assure recovery.^{13,17-19} Test of reversibility to beta-agonist was performed on subjects whose baseline FEV₁ was $<70\%$ of predicted by repeating spirometry 15 minutes following salbutamol (GlaxoSmithKline, China) given by nebulizer. A positive test of reversibility was defined as an increase in FEV₁ of $>12\%$ and >0.2 liters^{17,19}

Pulmonologists oversaw the pulmonary function testing and read the tests at Zhongshan Hospital, and an independent Pulmonary Function Testing oversight committee overread all tests and determined the final results.

The diagnosis of definite asthma was defined as both the presence of signs and symptoms of asthma as determined by the questionnaire, and the presence of bronchial hyperresponsiveness. Subjects who had a negative test of reversibility or had a negative MCT were considered not to have asthma. To avoid misclassification, women who had either an indeterminate test, or an FEV₁ fall between 16-19%, were not included in this analysis (n = 10).

Finally, the study population for this analysis consisted of 268 women, 106 of whom were diagnosed with definite asthma based on positive symptoms and a positive MCT or test of reversibility, and 162 of whom had asthma symptoms but a negative test and who were considered non-asthmatic.

The study was approved by the Institutional Review Board of (*removed for blinded review*), Shanghai Cancer Institute, Shanghai, China, and Zhongshan Hospital, Fudan University, Shanghai, China. All participants gave written informed consent.

We performed statistical analyses using the R package version 2.9.1 (<http://cran.us.r-project.org/>).²⁰ The association between each potential predictor variable and definite asthma was evaluated by univariate logistic regression analysis. Multivariable logistic regression analysis was performed to develop a scoring system for presence of asthma using

predictor variables from questionnaire responses alone. The relationships between potential predictor variables was assessed for data reduction to prevent overfitting.²¹ Self-reported ever asthma, ever wheezing or whistling in the chest, current medication use for asthma, self-reported ever allergic rhinitis, and family history of allergy were included in the multivariable logistic regression model based on the results from the cluster analysis and their clinical relevance to asthma.²¹ We included age in the prediction model as symptom perception and reporting, the co-occurrence of pulmonary co-morbidities, as well as the incidence of asthma may differ by age. Non-linearity of age was tested using restricted cubic splines and there was no statistically significant indication of non-linear effects by age. Thus, age was modeled as a continuous linear variable and all of the other predictors were modeled as dichotomous variables. Main effects were considered in multivariable model and interactions effects were not considered due to lack of power. The association between predictors and asthma in the model was assessed by the odds ratios and corresponding 95% confidence intervals (CI). The established predictive model provided the probability of asthma between 0 and 1 for each subject. The discrimination and the calibration of the model were used as measures to evaluate the predictive performance of the model.²² The discrimination ability of the model to distinguish subjects with asthma from non-asthmatic subjects was evaluated by the area under the receiver operating characteristic curve (AUC). Calibration provides an assessment of how far the predicted probabilities from the model are from the actual outcomes probabilities. In a plot of observed versus predicted probabilities, well-calibrated models have a slope of 1. To assess model overfit and estimate how well it will perform in a cohort of new subjects, we applied the bootstrapping method for internal validation. From bootstrapping technique, accuracy of validation estimates were evaluated by the calibration of the slope (shrinkage factor) and the root mean squared error of estimates.²¹

Finally, a nomogram was built from the above mentioned model to provide the probability of asthma at the individual level on the basis of response to variables from questionnaire. The nomogram is based on converting each regression coefficient (effect) in multivariable logistic regression model to a 0-100 scale which is proportional to the log odds.^{21,23} Regardless of statistical significance the effect with highest beta or log odds (absolute value) is assigned 100 points. For example, a patient with ever asthma is assigned 100 points, whereas a patient without gets 0 points. The points are added across independent variables to derive total points. The total points are converted to the linear predictor and then to predicted probabilities.²¹⁻²³

Results

The demographic characteristics of the 268 study subjects are shown in Table 1. Forty percent (106/268) of the women with signs and symptoms of asthma were diagnosed with definite asthma, confirmed by either MCT test or test of reversibility. There were no significant differences in age, education level, occupation, family income, menopausal status, body mass index (BMI), regular physical activity, or ever smoking between those with and without definite asthma.

Among the 268 women included in this analysis with symptoms of asthma (Table 2), 52% (n = 139) had wheezing or whistling in the chest in the past, 28% had wheezing or whistling in the chest in the past 12 months; 35% (n = 94) required medicine for asthma in the past, 14% (n = 37) were currently taking medicine for asthma. Among subjects without confirmed asthma, 6.9% (11/160) were currently taking asthma medication.

Of the 268 women, 32% (n=86) had asthma; 30% (n = 81) had doctor diagnosed asthma; and 18% (n = 48) had an attack of asthma in the past 12 months. Table 2 presents the association between the potential predictor variables and the occurrence of asthma in a univariate logistic regression analysis. Current or ever wheezing or whistling in the chest, current or ever

medication use for asthma, self-reported ever asthma, doctor diagnosed asthma or current attack of asthma were significantly associated with definite asthma. In addition, women who had symptoms of allergic rhinitis, had ever been diagnosed with allergic rhinitis, or had taken medication for allergic rhinitis were more likely to have definite asthma than women without the above features. A family history of allergy was also significantly associated with the occurrence of asthma.

The results of the multivariable logistic regression model for identifying individuals with asthma are shown in Table 3. The predictive model had reasonably good discrimination ability with the AUC: 0.75 (95% CI, 0.69 - 0.81). We performed an internal validation with the bootstrapping method. The bias corrected slope shrinkage factor was 0.87 and the maximum absolute error in predicted probability was 0.035 indicative of a robust model.

A nomogram was constructed based on the logistic regression model (Figure 2). Each predictor variable characteristic has a corresponding point value based on its position on the top point scale and contribution to the model. A total score was given to each subject by adding up the points. The probability of asthma for each subject can be calculated by the total score from the scale presented on the bottom line. A table was also provided to readily calculate the total point score (Table 4). For example, a women who is 50 years old (18 points), with a family history of allergy (26 point), with wheezing or whistling in the chest in the past (25 points), without asthma medication use (0 points), with self-reported ever asthma (100 points), with self-reported allergic rhinitis (81 points), is assigned a total score of 250, which translates into a 82% probability of having asthma. In addition, a website link is provided for use of the prediction model to calculate asthma probability (<http://data.vanderbilt.edu/nomogram/adult-asthma-probability>). This individual level estimation of asthma probability based on questionnaire response variables is intended to define asthma subjects for research or as a preliminary screen of asthmatics to decrease the number of study subjects for further testing.

Discussion

The criteria used to identify persons with asthma in epidemiologic studies are varied, and depending on the methodology used, can be challenging and resource consuming. Because of the need to improve the ability to define asthma in large epidemiologic studies using survey methods, we developed an algorithm for asthma case identification by incorporating a group of predictor variables, which were easily collected through a questionnaire survey. A nomogram was constructed based on this model, which can be used to assess the individual probability of asthma for research studies.

There is an ongoing debate about how to define the “gold standard” for the diagnosis of asthma. Physician diagnosed asthma is often used in epidemiologic studies. In this case, it is possible to underestimate the prevalence of asthma related to access to health care, the requirement of symptom reporting and perception, and the different diagnostic criteria used by physicians.^{24,25} The reporting of a single sign or symptom of asthma, as is evidenced in this study in which over 40% of the women who had at least one sign and/or symptom of asthma didn't have asthma (Table 2), can overestimate the prevalence of asthma. As airway hyperresponsiveness is a fundamental characteristic of asthma, one diagnostic approach has been the combination of respiratory symptoms with the presence of airway hyperresponsiveness measured with MCT test.^{13,26,27} However, not only can MCT generate a false negative diagnosis of asthma,²⁸⁻³⁰ it is costly and time consuming to conduct in large population-based studies.^{17,31} In the SWAAS investigation, lung function testing was not performed among subjects without asthma related signs or symptoms, or in subjects who met the criteria for alternate diagnoses, such as COPD or chronic bronchitis.

In our model, we have demonstrated that a combination of weighted signs and symptoms of asthma and atopy are closely associated with the presence of asthma, as confirmed by either a positive methacholine challenge test, or test of reversibility. Consistent with other investigations,^{28,32} the predictor variable “self-reported ever asthma”, defined by the positive response to the question “have you ever had asthma?” was one of the strongest predictor variables for identifying definite asthma in this study. “Wheezing or whistling in the chest” is the symptom frequently reported by subjects with asthma, which often overestimates the prevalence of asthma because of its low specificity.³³ Information on wheezing or whistling in the past, wheezing or whistling in the past 12 months, ever medication use for asthma and current medication use for asthma were all obtained in our study. These variables were observed to be closely associated with the presence of asthma, but were also present among a large proportion of women who did not have asthma, supporting the usefulness of combinations of symptom variables and related allergic diseases to discriminate the presence of asthma from the general population, as many women without confirmed asthma had some symptoms of asthma. Additional variables considered for our multivariable model included: “ever requiring asthma medicine,” “physician diagnosed asthma” and “symptoms of being woken by shortness of breath in the last 12 months,” were highly correlated with asthma symptom variables specified for the model and therefore were not included. Our model consisted of age, family history, ever wheezing/whistling in the past, current asthma medication, “self-reported ever asthma” and “self-reported ever allergic rhinitis” which was a significant and important predictor for the presence of asthma, as has been shown in other studies.³⁴⁻³⁶

The asthma nomogram is a tool that provides a probability of asthma for an individual study subject, and could be more easily applied than a logistic regression equation in a field investigation. Although several algorithms for asthma diagnosis have been previously developed in several European cohorts,^{33,37} this model is useful in large population-based epidemiologic studies in two ways: first, it predicts asthma risk in adults using a combination of well-validated weighted variables and an established cohort without requiring the testing of airways hyperresponsiveness; second, the nomogram and the provided on-line tool make it easy to understand and to use for estimation of individual probability.

Several potential limitations need to be considered in this study. First, variables in this prediction rule were obtained from women aged 40 to 69 years old in Shanghai China, therefore, the nomogram may not be generalizable to individuals outside this region, gender, or age range, and requires validation in other populations. We plan on validating the model in the same population during the planned second follow-up of this cohort, but that will not address the generalizability in populations that include men, broader age ranges, and other races. Although there is detailed information on all study subjects including confirmation of the diagnosis of asthma by MCT or test of reversibility, the study population is relatively small.

In summary, using validated questionnaire data and confirmatory testing of bronchial hyperresponsiveness to ascertain presence of asthma, a nomogram was developed in order to assess the individual probability of asthma in an adult population using combinations of responses based only on questionnaire data. While this model requires validation in other cohorts, it has the potential to be useful for identifying asthma in large population-based epidemiologic studies in which it is impractical and costly to conduct definitive MCT or test of reversibility on all study subjects.

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Figure 1. Flow diagram of the parent study cohort and inclusion/exclusion criteria of our study population

Figure 2. Nomogram to estimate individual asthma probability

The nomogram was constructed based on logistic regression model for outcome of definite asthma. Each predictor variable characteristic has a corresponding point value based on its position on the top point scale and contribution to the model. The probability of asthma for each subject is calculated by adding of the points for each variable to obtain a total point value which corresponds to a probability of asthma from the scale presented on the bottom line <http://data.vanderbilt.edu/nomogram.net/adult-asthma-probability>.

Table 1

Demographic characteristics of the 268 women comprising the study population from the Shanghai Women's Asthma and Allergy Study

Demographic Characteristic	Asthma (n=106)	No asthma (n=162)	All subjects (n=268)
Age (Mean in years $\pm$ SD [*])	51.70 $\pm$ 8.69	50.72 $\pm$ 8.14	51.10 $\pm$ 8.36
BMI (Mean kg/m ² $\pm$ SD [*])	24.65 $\pm$ 3.97	24.38 $\pm$ 3.21	24.48 $\pm$ 3.52
Education, n (%)			
High school/above	45 (42.45)	83 (51.23)	128 (47.76)
Middle school/less	61 (57.55)	79 (48.77)	140 (52.24)
Marital status, n (%)			
Presently married	99 (94.29)	154 (96.25)	253 (95.47)
Live alone	6 (5.71)	6 (3.75)	12 (4.53)
Occupation, n (%)			
Professional	26 (24.53)	55 (33.95)	81 (30.22)
Clerical	26 (24.53)	29 (17.90)	55 (20.52)
Farmer/worker	54 (50.94)	78 (48.15)	132 (49.25)
Family income, n (%)			
Low	27 (25.47)	32 (19.57)	59 (22.01)
Middle	38 (35.85)	71 (43.83)	109 (40.67)
High	41 (38.68)	59 (36.42)	100 (37.31)
Menopausal status, n (%)			
Pre menopause	59 (55.66)	92 (56.79)	151 (56.34)
Post menopause	47 (44.34)	70 (43.21)	117 (43.66)
Regular physical activity [†] , n (%)	34 (32.08)	59 (36.42)	93 (34.70)
Ever smoker, n (%)	4 (3.77)	3 (1.85)	7 (2.61)

* SD, standard deviation

[†] Regular physical activity is defined as at least once a week for more than 3 months, continuously over the past 5 years.

Table 2

The association between potential predictor variables derived from the asthma and allergy screening questionnaire, and the presence of confirmed asthma in the study population of 268 women from the Shanghai Women's Asthma and Allergy Study

Asthma Predictor Variable	Confirmed Asthma n (%)	OR (95%CI)
Ever wheezing or whistling in the chest		
No (n = 129)	33 (25.58)	1.00*
Yes (n = 139)	73 (52.52)	3.22 (1.92 - 5.40)
Wheezing or whistling in last 12 months		
No (n = 192)	69 (35.94)	1.00*
Yes (n = 76)	37 (48.68)	1.69 (0.99 - 2.90)
Ever requiring asthma medicine		
No (n = 173)	50 (28.90)	1.00*
Yes (n = 94)	56 (59.57)	3.62 (2.14 - 6.14)
Currently taking asthma medicine		
No (n = 227)	78 (34.36)	1.00*
Yes (n = 37)	26 (70.27)	4.54 (2.12 - 9.62)
Self-reported ever asthma		
No (n = 181)	49 (27.72)	1.00*
Yes (n = 86)	56 (65.12)	5.03 (2.84 - 8.54)
Physician diagnosed asthma		
No (n = 182)	50 (27.47)	1.00*
Yes (n = 81)	51 (62.96)	4.48 (2.57 - 7.83)
Attack of asthma in last 12 months		
No (n = 219)	75 (34.25)	1.00*
Yes (n = 48)	30 (62.50)	3.20 (1.67 - 6.11)
Woken by shortness of breath in last 12 months		
No (n=240)	92 (38.33)	1.00*
Yes (n=27)	13 (48.15)	1.49 (0.67 - 3.32)
Ever symptoms of allergic rhinitis		
No (n = 184)	63 (34.24)	1.00*
Yes (n = 84)	43 (51.19)	2.01 (1.19 - 3.41)
Allergic rhinitis to pollen, dust or animal hair		
No (n = 221)	78 (35.29)	1.00*
Yes (n = 39)	23 (58.97)	2.63 (1.32 - 5.28)
Self-reported ever hay fever or allergic rhinitis		
No (n = 209)	69 (32.54)	1.00*
Yes (n = 58)	37 (63.79)	3.65 (1.99 - 6.71)
Ever taking medicine for allergic rhinitis or hay fever		
No (n = 210)	74 (35.24)	1.00*
Yes (n = 58)	32 (55.17)	2.26 (1.25 - 4.08)

Asthma Predictor Variable	Confirmed Asthma n (%)	OR (95%CI)
Family history of allergy		
No (n = 174)	60 (34.48)	1.00*
Yes (n = 94)	46 (48.94)	1.82 (1.09 – 3.04)

* Reference group

Table 3

Results of the multivariable logistic regression model for identifying asthma among adult subjects of the Shanghai Women's Asthma and Allergy Study

Predictor Variables	Estimated regression coefficient	Estimated odds ratio	95%CI	P value
Age, every 10 year increment	0.22	1.24	0.89 – 1.73	0.20
Having a family history of allergy	0.33	1.40	0.78 – 2.51	0.26
Ever wheezing or whistling	0.32	1.38	0.71 – 2.67	0.34
Currently requiring asthma medication	0.23	1.26	0.50 – 3.17	0.62
Self-reported ever asthma	1.27	3.57	1.72 – 7.41	0.0006
Self-reported ever allergic rhinitis	1.03	2.80	1.41 – 5.56	0.0033

Intercept of the model: 0.64. The area under the ROC curve: 0.75 (95% CI, 0.69 - 0.81)

Table 4

Points scoring system for the predictor variables and the probability of asthma at different total point scores

Predictor variables	Points assigned
Age	$(\text{Age}-40)*1.75$
Family history of allergy	+ 26
Ever wheezing	+ 25
Current asthma medication use	+ 18
Ever asthma	+ 100
Ever allergic rhinitis	+ 81
Total point score	Probability of asthma (%)
0	16
50	26
100	40
150	55
200	70
250	82
300	89

A total point score for a given patient is obtained by summing the points for each predictor variable. The points assigned to each predictor variable are based on the top line of the nomogram. The probability of asthma for the patient is given on the bottom line of the nomogram (Figure 2).