
Development of a nomogram for identification of asthma among adults in epidemiologic studies

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Background: The criteria used to identify persons with asthma in epidemiologic studies are varying and, depending on the method used, can be challenging and resource consuming.

Objective: To develop a nomogram (scoring system) to identify adult patients with asthma using a combination of variables collected via a validated questionnaire.

Methods: We studied the first 268 women aged 40 to 69 years in the Shanghai Women's Asthma and Allergy Study who reported signs and symptoms of asthma and underwent either methacholine challenge testing or test of reversibility during the asthma screening survey between 2003 and 2007. These women were defined as having definite asthma ($n = 106$) or not ($n = 162$). Multivariable logistic regression analysis was performed to develop a predictive model for identifying asthma using survey information alone.

Results: Clinically relevant questions were used for the predictive multivariable logistic regression model and included the following: ever wheezing or whistling in the chest, current medication use for asthma, self-reported ever asthma, self-reported ever allergic rhinitis, family history of allergy, and age. The area under the receiver operating characteristic curve of the prediction model was 0.75 (95% confidence interval, 0.69–0.81). A nomogram was developed to assess the individual probability of asthma based on individually weighted variables in the predictive model.

Conclusions: In clinical or epidemiologic studies, this asthma nomogram could be used as a tool to assess the probability of asthma for an individual patient by incorporating asthma-related predictor variables obtained through a field questionnaire.

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INTRODUCTION

Asthma is a serious health problem with increased prevalence and incidence in recent decades in both children and adults. Identification of individuals likely to have asthma is a key step in asthma investigations. Epidemiologic investigations

have used 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.

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 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,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 epidemiologic studies of adult asthma, such as the

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Shanghai Women's Asthma and Allergy Study (SWAAS) and others.^{11,13}

Methacholine challenge testing (MCT) and/or test of reversibility to short-acting β -agonists are objective measurements used to assess bronchial hyperresponsiveness. However, there are practical limitations to performing these tests because they are 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 physiologic testing, and questions regarding whether MCT should even represent a criterion standard, questionnaires remain the principal instrument used to identify asthma in large population-based, epidemiologic studies.

Although most previously 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 based on their predictive value and to avoid the use of laboratory testing of bronchial hyperresponsiveness.

METHODS

From more 65,000 women enrolled in SWAAS, a prospective incidence study ongoing in Shanghai, China, the first 268 women who completed both the questionnaire survey and pulmonary function testing (PFT) were included in the present study. The objectives and design of 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 to 69 years from 7 urban districts of Shanghai were recruited to participate in the initial asthma screening survey, with an

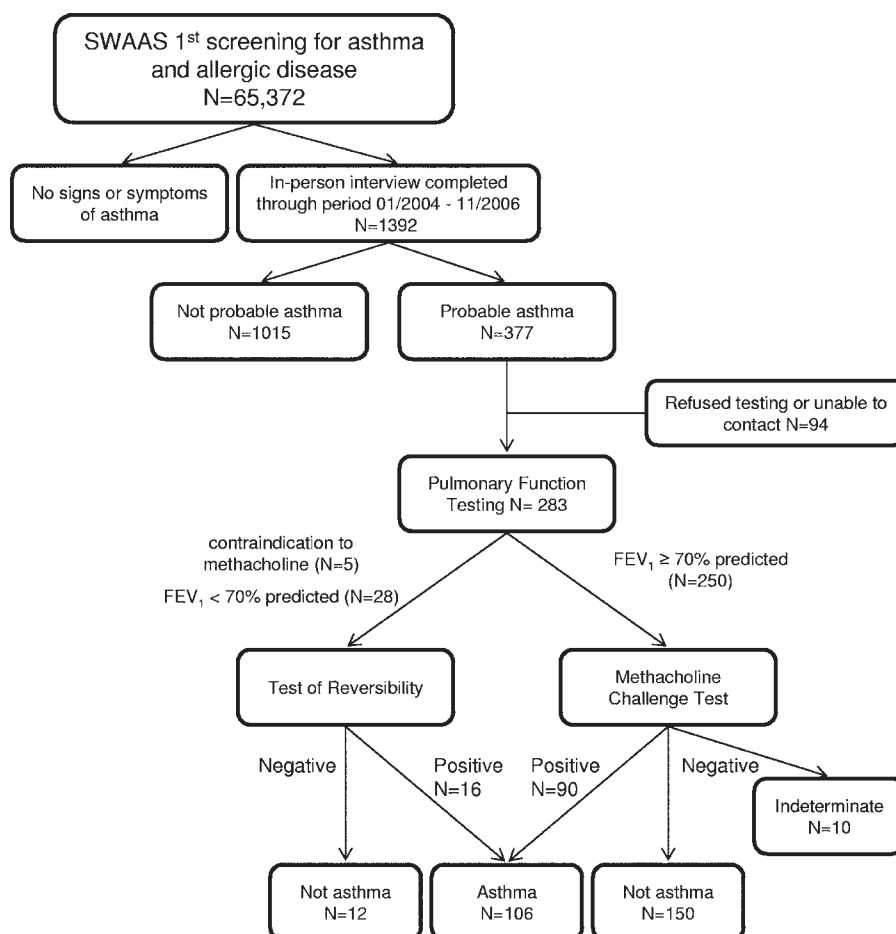


Figure 1. Flow diagram of the parent study cohort and inclusion and exclusion criteria of our study population. FEV₁ indicates forced expiratory volume; SWAAS, Shanghai Women's Asthma and Allergy Study.

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 the Shanghai Cancer Institute through an in-person home interview.¹³ Study participants were referred for MCT or test of reversibility at Zhongshan Hospital, Fudan University, to confirm the diagnosis of asthma if the individual 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 patients did not undergo MCT because of contraindications. Lung function testing was performed on 278 women.

The standard American Thoracic Society/European Respiratory Society protocol was used for MCT. In addition, all PFT results 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 patient. Spirometry was performed according to the body temperature and pressure standard convention with a spirometer (Jaeger Co., Hoechberg, Germany; and ASTOGRAPH TCK-6000M, Chest Corporation, Tokyo, Japan), which was calibrated and maintained to acceptable respiratory function laboratory standards.¹⁶ Before spirometric testing, patients were asked to withhold bronchodilator medications and those medications that interfere with methacholine. The following parameters were measured: forced expiratory volume in 1 second (FEV_1), forced vital capacity, forced expiratory flow at 25% to 75%, peak expiratory flow rate, and flow volume loops. These parameters were measured 3 times consecutively, and FEV_1 values had to be within 5% to be considered valid. For the analysis, the parameters from the test associated with the highest FEV_1 were used.

The MCT was performed if the baseline FEV_1 was 70% or more of predicted. Two-fold incremental concentrations of methacholine chloride (Tokyo Chemical Industry Co Ltd, Tokyo Kasei, Japan) reconstituted with physiologic saline were prepared from 0.015 to 0.96 mg/mL. Methacholine was inhaled with a synchronized nebulizer/dosimeter (Methapharm Inc, Coral Springs, Florida). 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 result was defined as a 20% decrease from baseline FEV_1 . After testing, patients received salbutamol, and spirometry was repeated to ensure recovery.^{13,17–19} Test of reversibility to β -agonist was performed on patients whose baseline FEV_1 was less than 70% of predicted by repeating spirometry 15 minutes after salbutamol (GlaxoSmithKline, Beijing, China) given by nebulizer.

A positive test of reversibility result was defined as an increase in FEV_1 of greater than 12% and greater than 0.2 L.^{17,19}

Pulmonologists oversaw the PFT and read the test results at Zhongshan Hospital, and an independent PFT oversight committee reread all test results 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. Patients who had a negative test of reversibility result or had a negative MCT result were considered not to have asthma. To avoid misclassification, women who had either an indeterminate test result or an FEV_1 decrease between 16% and 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 as having definite asthma based on positive symptoms and a positive MCT or test of reversibility result and 162 of whom had asthma symptoms but a negative test result and who were considered nonasthmatic.

The study was approved by the institutional review board of the 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://www.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 the presence of asthma using predictor variables from questionnaire responses alone. The relationships among potential predictor variables were 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 because symptom perception and reporting, the co-occurrence of pulmonary comorbidities, and the incidence of asthma may differ by age. Nonlinearity of age was tested using restricted cubic splines, and there was no statistically significant indication of nonlinear 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 the multivariable model, and interactions effects were not considered because of lack of power. The association between predictors and asthma in the model was assessed by the odds ratios and corresponding 95% confidence intervals (CIs). The established predictive model provided the probability of asthma between 0 and 1 for each study participant. 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 patients with asthma from nonasthmatic patients was

evaluated by the area under the receiver operating characteristic curve. Calibration provides an assessment of how far the predicted probabilities from the model are from the actual outcomes probabilities. In a plot of observed vs 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 patients, we applied the bootstrapping method for internal validation. From the bootstrapping technique, accuracy of validation was 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 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- to 100-point scale, which is proportional to the log odds.^{21,23} Regardless of statistical significance, the effect with highest β or log odds (absolute value) is assigned 100 points. For example, a patient with ever asthma is assigned 100 points, whereas a patient without is assigned 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 participants are given in Table 1. A total of 106 of the 268 women (40%)

with signs and symptoms of asthma were diagnosed as having definite asthma, confirmed by either MCT or test of reversibility. No significant differences were found in age, education level, occupation, family income, menopausal status, body mass index, 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), 139 (52%) had wheezing or whistling in the chest in the past, 76 (28%) had wheezing or whistling in the chest in the past 12 months, 94 (35%) required medicine for asthma in the past, and 37 (14%) were currently taking medicine for asthma. Among patients without confirmed asthma, 11 of 160 (6.9%) were currently taking asthma medication.

Of the 268 women, 86 (32%) had asthma, 81 (30%) had physician-diagnosed asthma, and 48 (18%) 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, physician-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 as having allergic rhinitis, or had taken medication for allergic rhinitis were more likely to have definite asthma than women without these features. A family history of allergy was also significantly associated with the occurrence of asthma.

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 patients (n = 268)
Age, mean (SD), y	51.70 (8.7)	50.72 (8.1)	51.10 (8.4)
Body mass index, mean (SD)	24.65 (4.0)	24.38 (3.2)	24.48 (3.5)
Education, No. (%)			
High school or above	45 (42.4)	83 (51.2)	128 (47.8)
Middle school or less	61 (57.6)	79 (48.8)	140 (52.2)
Marital status, No. (%)			
Currently married	99 (94.3)	154 (96.2)	253 (95.5)
Live alone	6 (5.7)	6 (3.8)	12 (4.5)
Occupation, No. (%)			
Professional	26 (24.5)	55 (34.0)	81 (30.2)
Clerical	26 (24.5)	29 (17.9)	55 (20.5)
Farmer or worker	54 (50.9)	78 (48.2)	132 (49.2)
Family income, No. (%)			
Low	27 (25.5)	32 (19.6)	59 (22.0)
Middle	38 (35.8)	71 (43.8)	109 (40.7)
High	41 (38.7)	59 (36.4)	100 (37.3)
Menopausal status, No. (%)			
Before menopause	59 (55.7)	92 (56.8)	151 (56.3)
After menopause	47 (44.3)	70 (43.2)	117 (43.7)
Regular physical activity, ^a No. (%)	34 (32.1)	59 (36.4)	93 (34.7)
Ever smoker, No. (%)	4 (3.8)	3 (1.8)	7 (2.6)

Abbreviations: SD, standard deviation.

^a Regular physical activity is defined as at least once a week for more than 3 months continuously during the past 5 years.

Table 2. Association Among 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, No. (%)	OR (95% CI)
Ever wheezing or whistling in the chest		
No (n = 129)	33 (25.6)	1.00 [Reference]
Yes (n = 139)	73 (52.5)	3.22 (1.92–5.40)
Wheezing or whistling in last 12 months		
No (n = 192)	69 (35.9)	1.00 [Reference]
Yes (n = 76)	37 (48.7)	1.69 (0.99–2.90)
Ever requiring asthma medicine		
No (n = 173)	50 (28.9)	1.00 [Reference]
Yes (n = 94)	56 (59.6)	3.62 (2.14–6.14)
Currently taking asthma medicine		
No (n = 227)	78 (34.4)	1.00 [Reference]
Yes (n = 37)	26 (70.3)	4.54 (2.12–9.62)
Self-reported ever asthma		
No (n = 181)	49 (27.7)	1.00 [Reference]
Yes (n = 86)	56 (65.1)	5.03 (2.84–8.54)
Physician diagnosed asthma		
No (n = 182)	50 (27.5)	1.00 [Reference]
Yes (n = 81)	51 (63.0)	4.48 (2.57–7.83)
Attack of asthma in last 12 months		
No (n = 219)	75 (34.2)	1.00 [Reference]
Yes (n = 48)	30 (62.5)	3.20 (1.67–6.11)
Woken by shortness of breath in last 12 months		
No (n = 240)	92 (38.3)	1.00 [Reference]
Yes (n = 27)	13 (48.2)	1.49 (0.67–3.32)
Ever symptoms of allergic rhinitis		
No (n = 184)	63 (34.2)	1.00 [Reference]
Yes (n = 84)	43 (51.2)	2.01 (1.19–3.41)
Allergic rhinitis to pollen, dust, or animal hair		
No (n = 221)	78 (35.3)	1.00 [Reference]
Yes (n = 39)	23 (59.0)	2.63 (1.32–5.28)
Self-reported ever hay fever or allergic rhinitis		
No (n = 209)	69 (32.5)	1.00 [Reference]
Yes (n = 58)	37 (63.8)	3.65 (1.99–6.71)
Ever taking medicine for allergic rhinitis or hay fever		
No (n = 210)	74 (35.2)	1.00 [Reference]
Yes (n = 58)	32 (55.2)	2.26 (1.25–4.08)
Family history of allergy		
No (n = 174)	60 (34.5)	1.00 [Reference]
Yes (n = 94)	46 (48.9)	1.82 (1.09–3.04)

Abbreviations: CI, confidence interval; OR, odds ratio.

The results of the multivariable logistic regression model for identifying individuals with asthma are given in Table 3. The predictive model had reasonably good discrimination ability with an area under the receiver operating characteristic curve of 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 patient by adding the points. The probability of asthma for each patient 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), and 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 Web site link is provided for use of the prediction model to calculate asthma probability (<http://nomogram.net/adult-asthma-probability>). This individual-level estimation of asthma probability based on questionnaire response variables is intended to define asthma patients for research or as a preliminary screen of asthmatic patients to decrease the number of study participants for further testing.

DISCUSSION

The criteria used to identify persons with asthma in epidemiologic studies are varied and, depending on the method 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 criterion 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 more than 40% of the women who had at least 1 sign and/or symptom of asthma did not have asthma (Table 2), can overestimate the prevalence of asthma. Because airway hyperresponsiveness is a fundamental characteristic of asthma, 1 diagnostic approach has been the combination of respiratory symptoms with the presence of airway hyperresponsive-

Table 3. Results of the Multivariable Logistic Regression Model for Identifying Asthma Among Adult Participants in the Shanghai Women's Asthma and Allergy Study^a

Predictor variable	Estimated regression coefficient	Estimated OR (95% CI)	P value
Age, every 10-year increment	0.22	1.24 (0.89–1.73)	.20
Having a family history of allergy	0.33	1.40 (0.78–2.51)	.26
Ever wheezing or whistling	0.32	1.38 (0.71–2.67)	.34
Currently requiring asthma medication	0.23	1.26 (0.50–3.17)	.62
Self-reported ever asthma	1.27	3.57 (1.72–7.41)	<.001
Self-reported ever allergic rhinitis	1.03	2.80 (1.41–5.56)	.003

Abbreviations: CI, confidence interval; OR, odds ratio.

^a Intercept of the model was 0.64. The area under the receiver operating characteristic curve was 0.75 (95% CI, 0.69–0.81).

ness measured by MCT.^{13,26,27} However, not only can MCT generate a false-negative diagnosis of asthma,^{28–30} it also 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 patients without asthma-related signs or symptoms or in those who met the criteria for

alternate diagnoses, such as chronic obstructive pulmonary disease 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 positive results on MCT or test of reversibility. Consistent

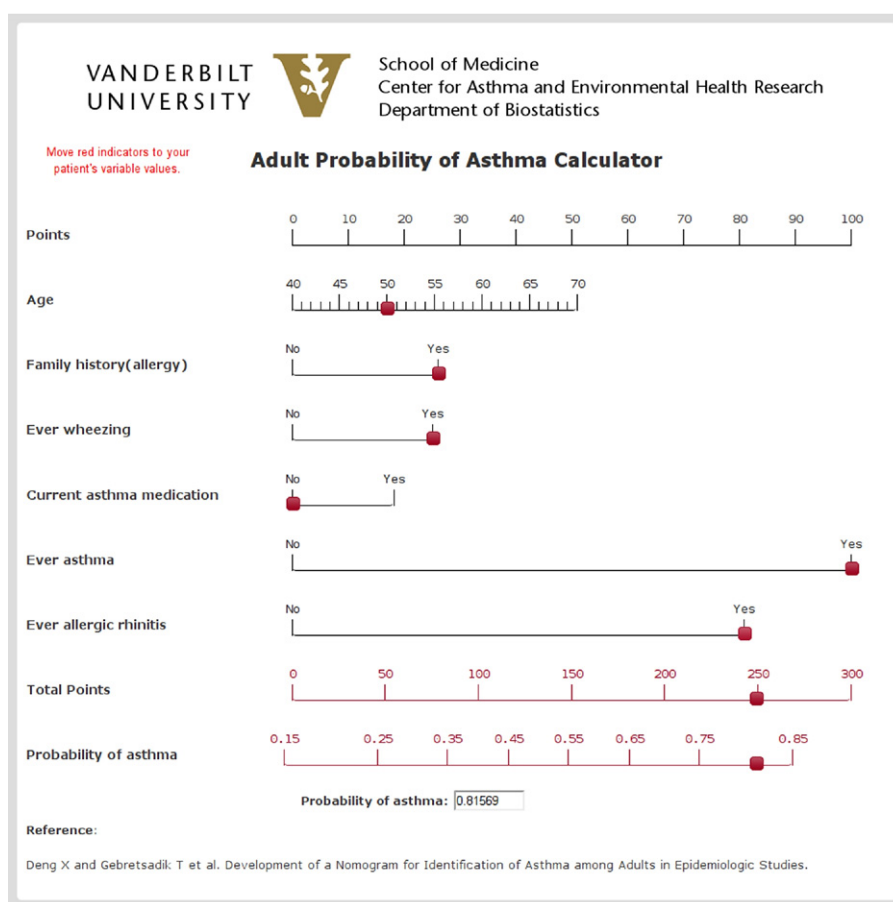


Figure 2. Nomogram to estimate individual asthma probability. The nomogram was constructed based on logistic regression model for outcome of definite asthma. Each predictor variable characteristic has a corresponding point value based on its position on the top point scale and contribution to the model. The probability of asthma for each patient is calculated by adding of the points for each variable to obtain a total point value that corresponds to a probability of asthma from the scale presented on the bottom line (<http://nomogram.net/adult-asthma-probability>).

Table 4. Point Scoring System for the Predictor Variables and the Probability of Asthma at Different Total Point Scores^a

Predictor variable	Points assigned
Age	$(\text{Age} - 40) \times 1.75$
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 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 part of the nomogram. The probability of asthma for the patient is given on the bottom part of the nomogram (Figure 2).

with other investigations,^{28,32} the predictor variable self-reported ever asthma, defined as a positive response to the question “Have you ever had asthma?” was 1 of the strongest predictor variables for identifying definite asthma in this study. Wheezing or whistling in the chest is the symptom frequently reported by patients 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 because many women without confirmed asthma had some symptoms of asthma. Additional variables considered for our multivariable model, including 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 or 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 patient 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 co-

horts,^{33,37} this model is useful in large population-based, epidemiologic studies in 2 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 online 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 in Shanghai, China; therefore, the nomogram may not be generalizable to individuals outside this region, sex, 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 participants, 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 to assess the individual probability of asthma in an adult population using combinations of responses based only on questionnaire data. Although 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 participants.

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