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Development and validation of a prediction model for airflow obstruction in older Chinese: Guangzhou Biobank Cohort Study

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ABSTRACT

Objective: To develop and validate a prediction model for airflow obstruction (AO) in older Chinese.
Methods.
Design: Multivariable logistic regression analysis in large population cohort of Chinese aged ≥50 years.
Participants: Model development: 8762 Chinese aged ≥50 years were selected from the early phase recruits to the Guangzhou Biobank Cohort Study (GBCS) (recruited from September 2003 to May 2006). Internal validation: 100 bootstrap samples drawn with replacement from the development sample. External validation: 8395 Chinese aged ≥50 years from later phase GBCS (recruited from September 2006 to January 2008).
Outcomes: AO was defined by a forced expiratory volume in 1 s/forced vital capacity ratio < lower limits of normal.
Results: 839 (9.6%) and 764 (9.1%) individuals had AO in the development and temporal validation samples respectively. The predictors in the prediction model included sex, age, body mass index groups, smoking status, presence of respiratory symptoms, and history of asthma. Model development and validation was stratified by sex. Model performance including calibration (calibration-in-the-large −0.017 vs. −0.157; and calibration slope 0.88 vs. 1.02), discrimination (C-statistic 0.72 vs. 0.63 with 95% confidence interval 0.69–0.75 vs. 0.62–0.73) and clinical usefulness (decision curve analysis) in the external temporal validation sample were more satisfactory in men than that in women. Prediction models with risk thresholds (13% in men and 7% in women) and easy-to-use nomograms were developed to assess the probability of AO.
Conclusion: The diagnostic models based on readily available epidemiologic and clinical information with satisfactory performance can assist physicians to identify older individuals at high risk of AO and may improve the efficiency of spirometry for active case finding. Further validation beyond the Chinese population is warranted.

1. Introduction

1.1. Background and objectives

Chronic obstructive pulmonary disease (COPD), characterised by airflow obstruction (AO), is a worldwide public health problem that is largely undiagnosed. Individuals with undiagnosed COPD have an increased risk of exacerbation, pneumonia, and death [1].

The China Pulmonary Health (CPH) study found the prevalence of spirometry-defined COPD (AO) during 2012–2015 was 8.6% in 57779 Chinese individuals [2]. Only 2.6% of these were aware of their respiratory condition [2], which was much lower than those in Western population (11%–54%) [3,4]. Screening to identify undiagnosed COPD patients is recommended by the Global Initiative for Chronic Obstructive Lung Disease (GLOD) [5] and the Chinese government [6]. GOLD advocates active case finding i.e., performing spirometry for symptomatic patients or individuals with high risk. The 13th Five-year Plan for Sanitation and Health of the People's Republic China promotes

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screening spirometry as a regular health test. However, some international guidelines [7] recommend against screening, partly because of high false positive rates and the large numbers needed to be screened to identify a case. These inefficiencies could be minimized by using a prediction model which could identify the high risk groups for spirometry. Although a number of risk prediction models exist, model development methods are not always transparent [8] and few have undertaken internal validation [9,10]. Two existing risk prediction models are of high quality [11,12], but were developed in Western populations. The prevalence and characteristics of undiagnosed COPD, the risk factor profile and access to medical resources are quite different in non-Western countries [3]. Existing models may therefore have limited practical application in non-Western population settings.

We aimed to develop and validate a diagnostic model for predicting risk of AO using readily available epidemiologic and clinical information from a large Chinese cohort. An easy-to-use nomogram of this model is presented for practical application.

2. Methods

This paper is reported in line with the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement [13].

3. Source of data

Baseline data from Guangzhou Biobank Cohort Study (GBCS) were used for the development and validation of the equation for AO risk prediction. GBCS phase 1 and phase 2 subjects (recruited from September 2003 to May 2006) were included in the development sample. Bootstrap samples drawn with replacement from the development sample were used for internal validation. GBCS phase 3 participants (recruited from September 2006 to January 2008) were used for external temporal validation. The candidate variables were different in these 2 samples. For each individual, all potential predictors and the outcome (spirometry) were measured in the same morning.

4. Participants

GBCS, a three-way collaboration among Guangzhou No. 12 Hospital, the Universities of Birmingham and Hong Kong, recruited 30430 permanent Guangzhou residents aged 50 years or older from 2003 to 2008 [14]. All participants provided written consent before participation. Adults were ineligible if they were non-ambulatory, receiving chemotherapy or radiotherapy for cancer, or dialysis for renal failure. After excluding 13273 GBCS participants; 739 without spirometry and 12534 whose spirometry was invalid, based on criteria reported elsewhere [15], we included 17157 participants in the present study.

5. Outcome

The outcome of interest was AO which was defined as the ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) <lower limits of normal (LLN). The LLN of FEV_1/FVC was derived using the Global Lung Function Initiative (GLI) 2012 reference equations for South East Asians developed by Quanjer, Philip H [16]. We chose this criterion of AO instead of the fixed ratio definition (FEV_1/FVC <0.70) to minimize potential misclassification of subjects with normal pulmonary function. However, we did sensitivity analysis based on the fixed ratio definition for comparability with other studies. We used the equation developed by Ip [17] to define LLN in all previous GBCS manuscripts, so we also undertook sensitivity analysis based on this definition. Spirometry was done with a pneumotachograph (Chestgraph HI-701, Chest MI Inc, Tokyo, Japan) in phase 1, a turbine flowmeter (Cosmed microQuark, Rome, Italy) in phase 2 and two ultrasonic flowmeters (ndd Medical Technologies Easy-on PC; Zurich, Switzerland) in phase 3 [15, 18]. In brief, the pulmonary function tests with at least three manoeuvres, were conducted in a standing position following standard procedures. The best measure of FEV_1 and FVC were recorded. The trained interviewers who conducted the spirometry were blinded to the candidate variables collected by other interviewers [14].

6. Predictors

We selected 16 candidate variables based on a review of previous relevant studies and components of existing models [8,10–12,19,20]. These were extracted from the GBCS database (Table 1). Trained interviewers blinded to spirometry measurements used a standardized computer-based questionnaire to collect information on demographic characteristics (sex, age, occupation, education level), occupational dust, home dust (biomass cooking fuel) and passive smoking exposure, lifestyle (smoking status with pack-years and alcohol drinking status), self-reported respiratory symptoms (cough, phlegm, wheezing and dyspnea (based on the British modified Medical Research Council (mMRC) dyspnea scale)), personal disease history (asthma, hypertension, diabetes mellitus (DM)), and self-reported antihypertensive and antidiabetic medication. Standard physical examination included standardized measurement of body weight, height and blood pressure. Blood glucose and lipids were assayed after an overnight (>8 h) fast. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or self-reported use of antihypertensive medication. DM was defined as fasting glucose ≥7.0 mmol/L and/or self-reported DM.

7. Sample size

We included 17157 GBCS participants with valid data from the entire cohort, of whom 1603 had AO. Our study had about 52 outcome outcome events per variable (EPV) in the development study and 764 events in the validation study, which far exceeded suggested minimum values for reliable prediction research [21].

8. Missing data

Because participants with valid or invalid spirometry data showed only slightly different results (Appendix table 1), we assumed missing spirometry data was likely to occur largely at random, meaning that our study sample was unlikely to be a biased subsample. Only 484 (2.8%) of 17157 participants with valid spirometry had missing data on some predictors. In these cses, multiple imputation using chained equations was performed using Stata/SE 15.1 to impute missing values (based on all other predictors). All variables considered in the original development and validation samples were considered in the imputation model. We used stacked data sets and implemented a weighted backward stepwise selection method for modelling. In internal validation, model selection was performed in each imputation set. The predictors selected differed slightly across imputation, and we chose variables which were selected in 90% of imputation sets. These variables were also the predictors selected in the stacked dataset. In external validation, the model performance of the model developed from the stacked dataset was tested in each imputation validation sample set. Rubin's rules were used to combine model performance from each of the 10 imputed data sets (internal or external validation) to obtain the average performances [22].

8.1. Statistical analysis methods

Linearity for continuous predictors (age and BMI) against the log odds of binary outcome (AO) were examined (Fig. Appendix Fig. 1, both P values for linear trend <0.0001). The plots of restrictive cubic spline function showed the odds ratio with 95% confidence interval (CI) of age and BMI for AO (Fig. Appendix Fig. 2). The linearity for BMI was weaker

Table 1
Characteristics of participants in the development and validation samples.

	Development sample	Validation sample	P value
Number	8762	8395	
Median Age (IQR), y	62.1 (56.7–67.7)	58.8 (54.0–65.8)	<0.001
Male, n (%)	2402 (27.4)	2096 (25.0)	<0.001
Education, n (%)			<0.001
≤Primary	3896 (44.5)	3117 (37.1)	
Middle school	4065 (46.4)	4569 (54.4)	
≥College	796 (9.1)	706 (8.4)	
Occupation, n (%)			<0.001
Manual	5260 (69.3)	2167 (26.2)	
Non-manual	2153 (28.4)	3901 (47.2)	
Others	182 (2.4)	2192 (26.5)	
Smoking, n (%)			<0.001
Never smoker	7025 (80.3)	6865 (82.3)	
Former smoker	864 (9.9)	627 (7.5)	
Current smoker (0–29 pack-years)	421 (4.8)	444 (5.3)	
Current smoker (≥30 pack-years)	442 (5.1)	403 (4.8)	
Dust exposure, n (%)			<0.001
No exposure	1932 (26.4)	2962 (38.3)	
Occupational or home exposure	3576 (49.0)	3676 (47.5)	
Occupational and home exposure	1798 (24.6)	1100 (14.2)	
Drinking, n (%)			
Never	7007 (80.3)	2284 (35.4)	<0.001
Former	191 (2.2)	237 (3.7)	
Current	1529 (17.5)	3937 (61.0)	
Median BMI (IQR), kg/m^2	23.6 (21.6–25.8)	23.7 (21.6–25.9)	0.06
BMI group, n (%)			0.22
Underweight	379 (4.3)	349 (4.2)	
Normal	4429 (50.6)	4171 (49.7)	
Overweight	3096 (35.4)	2979 (35.5)	
Obesity	845 (9.7)	886 (10.6)	
Self-reported respiratory symptoms, n (%)			<0.001
No symptom	7581 (88.3)	7279 (87.5)	
One symptom	848 (9.9)	823 (9.9)	
More than one symptom	153 (1.8)	218 (2.6)	
History of diseases			
Asthma, n (%)	144 (1.6)	101 (1.2)	0.02
Hypertension, n (%)	3777 (43.1)	3270 (39.0)	<0.001
DM, n (%)	1146 (13.1)	862 (10.3)	<0.001
Airflow obstruction, n (%)	839 (9.6)	764 (9.1)	0.43
Airflow obstruction*, n (%)	834 (9.5)	728 (8.7)	0.05

Abbreviations: IQR, interquartile range; BMI, body mass index; DM, Diabetes mellitus.
Dust exposure: occupational dust exposure and biomass cooking fuel exposure. Biomass cooking fuel: wood, charcoal and coal.
BMI group: Underweight: BMI<18.5 Normal: 18.5 ≤BMI < 24 kg/m^2 Overweight: 24 ≤BMI < 28 kg/m^2 Obesity: BMI ≥28 kg/m.^{2}.
Self-reported respiratory symptoms: presence of cough, phlegm, wheezing for three months per year, and/or dyspnea.
Dyspnea: the British modified Medical Research Council (mMRC) scale ≥2.
Hypertension: systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or self-reported use of antihypertensive medication.
DM: fasting glucose ≥7.0 mmol/L and/or self-reported DM.
Airflow obstruction: Forced expiratory volume in 1 s/forced vital capacity ratio < lower limits of normal.
Airflow obstruction*: Forced expiratory volume in 1 s/forced vital capacity ratio <0.70.
P values based on Pearson chi-squared test for categorical variables, and nonparametric equality-of-medians for continuous variables.

than that for age. Hence, age was treated as a continuous variable and the restricted cubic spline with 4 knots was used to treat BMI in model development to avoid information loss. Splines for BMI were prepared with knot placement based on the percentile distributions of these variables in men and women. We chose the number and location of knots used to fix splines in modelling according to the well-accepted recommendations [23,24]. Uncommon respiratory symptoms (self-reported cough (2.2%), phlegm (3.5%), wheezing (3.1%) and mMRC defined dyspnea (6.5%)) were combined into a three-levels predictor: no respiratory symptoms, one respiratory symptom and more than one respiratory symptom, which resulted in elimination of sparse categories [23]. Occupational dust exposure and home dust exposure were also combined into a three-level predictor (no dust exposure, occupational or home dust exposure, occupational and home dust exposure) to simplify the model and better assess the impact of dust exposure. All predictors were checked for extreme values to prevent undue leverage effects, and no extreme values were found.

9. Modelling approach

Multivariable logistic regression was used to estimate the regression coefficients of each predictor for AO. We included 9 candidate variables: demographic characteristics (sex and age), body mass index groups, socio-economic status (education level and occupation), dust exposure (occupational dust and/or home dust exposure (biomass cooking fuel including wood, charcoal and coal)), smoking status with pack-year, diagnosed asthma and respiratory symptoms. These were primarily chosen based on previous studies [8,10–12,19,20] and clinical expertise. Male sex showed reversed regression coefficients in the model for LLN defined AO (0.55, 95% CI 0.46–0.76) and the fixed ratio defined AO (1.37, 95% CI 1.08–1.72). The prevalence of AO was different in men (12.8%) and women (8.3%). So we stratified the analysis by sex for efficiencies of the model and to avoid obtaining opposite results.

Given the very large number of events (839 in development sample, 308 were men and 531 were women), we used a simple model specification strategy i.e., backward stepwise selection with $P < 0.01$. We created a simple 'stacked' data set that combines the multiple imputed data sets into one [25,26] with 24020 men records and 63600 women records. The weight was 0.1 for each participant. We restricted our modelling strategy to the main effects of predictors and did not consider interactions. Including an interaction term does not necessarily increase the performance of a model [23].

10. Internal validation

Internal validity was assessed with a bootstrapping procedure within each imputed data set to avoid overoptimistic performance estimates. The model developing process was repeated in 100 bootstrapping samples each with 2402 male records and 6360 female records drawn with replacement from each of 10 imputed development sample. The optimism in performance (concordance statistic (C- statistic)) was estimated as the difference of the performance of a model developed in the bootstrapped sample (bootstrap performance) and the performance of that model in the original sample (test performance). The optimism was estimated in each of the 100 bootstrap samples to obtain the mean estimate of the optimism. The optimism-corrected estimate of performance was obtained by subtracting the mean estimate of the optimism (C-statistic differences) from the C-statistic for the model in the development sample (apparent performance in original sample) [27]. All bootstrapped optimism performances in each imputed dataset were averaged to get the final model performance. The predicted probability for AO of each individual from the validation sample was calculated using the developed logistic model.

11. External validation

We assessed four measures for model performance [28] in the external temporal validation cohort: calibration (calibration-in-the-large and calibration slope) which reflects the agreement between the predicted probabilities and the observed outcomes; discrimination (C-statistic) which refers to the ability to differentiate

those with AO from those without AO, and clinical usefulness (decision-curve analysis to indicate net benefit across a plausible range of decision thresholds), which refers to the ability to make better decisions with the model than without it [29]. Next, the development and validation samples were combined to develop an updated version of the prediction model [30], after testing for effect differences between the two samples by statistical interaction terms.

All tests of significance were 2-tailed, with $P < 0.05$ as statistically significant. All analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria, www.r-project.org).

12. Results

12.1. Participants

Fig. 1 shows the flow of participants. The prevalence of AO was 9.6% (839/8762) (12.8% in men and 8.3% in women) and 9.1% (764/8395) (14.2% in men and 7.4% in women) in the development and validation samples, respectively (Fig. 1).

Table 1 shows that the characteristics of the validation sample were somewhat different from that of the development sample. The median age was 62.1 and 58.8 years in the development and validation samples, and 27.4% and 25% were men, respectively. Compared with the validation sample, people in the development sample had lower socioeconomic status (more manual occupations and lower educational level), were more likely to be smokers and never drinkers, had higher prevalence of dust exposure, hypertension and DM, and had lower prevalence of respiratory symptoms.

Model development Table 2 shows that the AO prevalence in men and women was significantly different by age, BMI groups and most of the variables except drinking status, occupation, DM and hypertension. The fixed ratio defined AO prevalence is similar to the LLN defined AO prevalence. Table Appendix 4TTThe variance-inflation factors (VIFs) of these variables ranged from 1.020 to 1.078, indicating limited collinearities in these models. The stacked method (weighted backward stepwise selection in the stacked multiple imputed data set) selected 6 predictors into the final prediction model from 9 candidate variables for both men and women (Table 3). These included age, smoking and drinking status, BMI, presence of respiratory symptoms and diagnosed asthma. When using the fixed ratio definition of AO, these 6 predictors remained in the model for women, and only drinking status was excluded in the model for men (Appendix table 5).

13. Model specification

Table 3 shows that the odds ratios were only slightly different in the development and validation samples for most of the predictors. Table 4 shows the equation with the predictors included in the updated prediction model. Fig. 2 shows an easy-to-use nomogram of this model and explanation of how to use the equation or nomogram to obtain the predicted probability of AO for an individual.

14. Model performance

The model in men had an acceptable discrimination (AUC 0.74, 95% CI 0.73–0.74) in the original sample and similar discrimination at internal validation (AUC 0.72). External validation showed similar performance (AUC 0.72, 95% CI 0.69–0.75) (Table 3). The discrimination of the model for women was less satisfactory (apparent AUC 0.63 (95% CI 0.63–0.64) and externally validated AUC 0.63 (95% CI 0.62–0.631)).

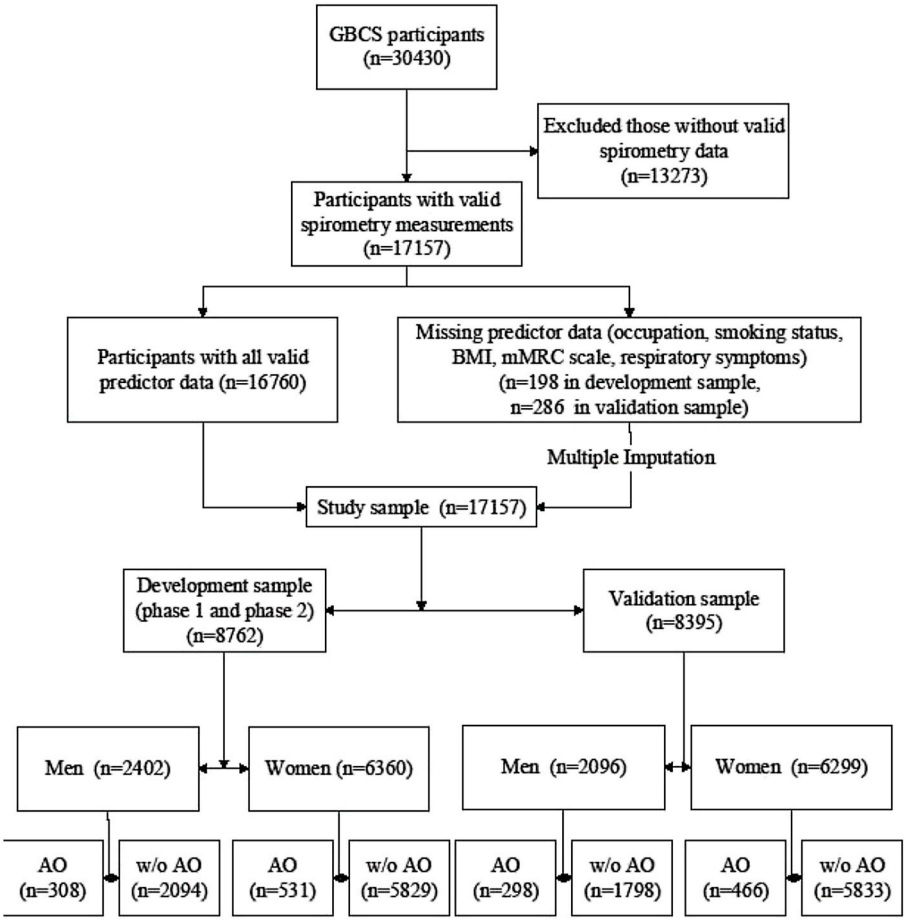
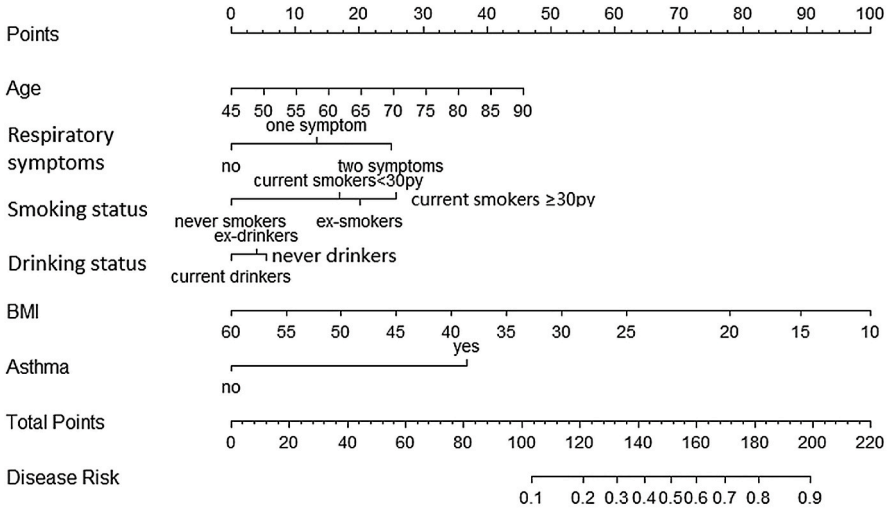
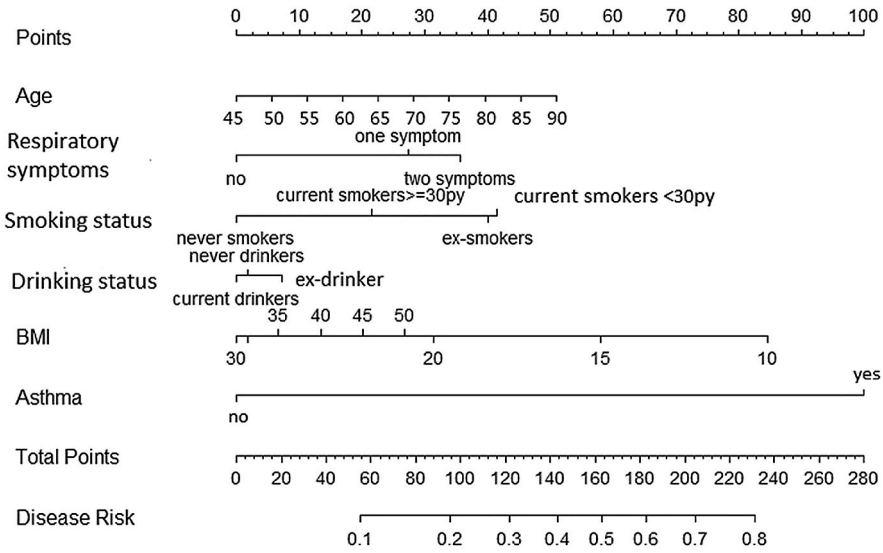


Fig. 1. Participant flow diagram.
Abbreviations: GBCS, Guangzhou Biobank Cohort Study; BMI, body mass index; mMRC, the British modified Medical Research Council; AO, airflow obstruction; w/o, without.
Airflow obstruction: Forced expiratory volume in 1 s/ forced vital capacity ratio < lower limits of normal.



A. Nomogram of the updated prediction model in men



B. Nomogram of the updated prediction model in women

Fig. 2. Nomogram of the updated prediction model for airflow obstruction in men and women. Instructions: Locate the individual's age on the age axis, draw a line straight upward to the Points axis to get the scores toward the probability of airflow obstruction. Repeat the process for each variable and sum the total score achieved for all predictors. Locate the total score on the Total points axis and draw a line straight down to figure out this individual's probability of having airflow obstruction.
Abbreviation: py: pack years; BMI: body mass index
Self-reported respiratory symptoms: cough, phlegm, wheezing for three months per year, and/or dyspnea
Dyspnea: the British modified Medical Research Council (mMRC) scale ≥2
Airflow obstruction: Forced expiratory volume in 1 s / forced vital capacity ratio < lower limits of normal.

Calibration plot for the developed model in external validation sample (Fig. 3 and Table 3) showed that the calibration-in-the-large (comparing the mean of all predicted risks with the mean observed risk) and the calibration slope were slightly deviating (−0.017 and 0.878 in men, −0.157 and 1.016 in women) from ideal values (0 and 1), indicating a good agreement between observed endpoints and predictions [28]. Appendix table 2 shows the sensitivity and specificity at different cut-off pointz. The cut-off point of 13% for men had the largest Youden's index, with sensitivity and specificity of 69% and 66% respectively. In women, a cut-off point of 8% had the largest Youden's index, with sensitivity and specificity of 48% and 71% respectively. To avoid missing too many women with high risk, we may put more weight on sensitivity by choosing a lower cut-off point for this model, using 7%, with resulting sensitivity of 60% and specificity of 59%. Clinical usefulness of the combined model shown in a decision curve (Fig. 4) indicated that the ability to find AO with this prediction model was better than without across a wide range of clinically plausible thresholds (around 4%–35%). The net benefit (NB) of 0.05 and 0.02 at the threshold probability of 13% and 7% (Appendix table 3) implied that comparing to conducting no spirometry test in men and women, conducting spirometry on the basis of the prediction model was the equivalent of a strategy that found 5 men and 2 women with AO per hundred patients without conducting any unnecessary spirometry. Appendix table 3 and Appendix Fig. 3 shows that the net reduction in interventions was about 29 and 12 per 100 male and female patients at the probability threshold of 13% and 7%. In other words, at this probability threshold, conducting spirometry on individuals on the basis of the prediction model was the equivalent of a strategy that reduced the spirometry test rate by 29% and 12% for men and women without AO, without increasing the number with AO who are not tested. When using the fixed ratio definition of AO, 12% and 6% were chosen as the risk threshold for men and women, respectively. The prediction models for fixed ratio defined AO had better discrimination (AUC 0.755, 95% CI 0.754–0.756 in men, AUC 0.733, 95% CI 0.730–0.736 in women), clinical usefulness (NB 0.08 in men and 0.02 in women) and calibration (Calibration-in-the-large 0.008 in men and 0.021 in women, calibration slope 0.912 in men and 1.098 in women)

Table 2
Prevalence of airflow obstruction in the development and validation sample.

Characteristics	Men				Women			
	Prevalence of AO in the development sample (n = 2402)		Prevalence of AO in the validation sample (n = 2096)		Prevalence of AO in the development sample (n = 6360)		Prevalence of AO in the validation sample (n = 6299)	
	% (No./Total)	P value	% (No./Total)	P value	% (No./Total)	P value	% (No./Total)	P value
Total	12.8 (308/2402)		14.2 (298/2096)		8.3 (531/6360)		7.4 (466/6299)	
Age group, n (%)		<0.001		<0.001		<0.001		<0.001
<60	6.5 (39/599)		9.7 (74/762)		6.6 (192/2906)		6.4 (251/3903)	
60–69.9	13.7 (172/1256)		15.4 (137/891)		9.4 (246/2625)		8.3 (136/1637)	
≥70	17.5 (97/554)		19.6 (87/443)		11.2 (93/829)		10.4 (79/759)	
Education, n (%)		0.05		<0.001		0.04		<0.001
≤Primary	15.4 (108/700)		21.0 (125/596)		9.2 (295/3195)		9.2 (231/2521)	
Middle school	11.8 (149/1262)		12.1 (144/1188)		7.5 (211/2802)		6.0 (202/3381)	
≥College	11.7 (51/436)		9.3 (29/311)		7.0 (25/359)		8.4 (33/395)	
Occupation, n (%)		0.85		0.001		0.34		0.07
Manual	13.6 (148/1086)		18.8 (109/579)		8.7 (361/4173)		8.5 (135/1588)	
Non-manual	12.8 (124/966)		12.7 (123/967)		8.3 (98/1186)		6.6 (195/2934)	
Others	14.3 (7/49)		12.2 (63/516)		12.0 (16/133)		7.6 (128/1676)	
Smoking, n (%)		<0.001		<0.001		<0.001		<0.001
Never smoker	6.8 (62/918)		7.6 (59/776)		8.0 (486/6105)		7.0 (428/6098)	
Former smoker	16.7 (125/750)		18.3 (100/547)		19.3 (22/114)		18.8 (15/80)	
Current smoker (0–29 pack-years)	14.6 (47/322)		9.7 (53/444)		18.4 (18/98)		21.4 (15/70)	
Current smoker (≥30 pack-years)	18.2 (74/407)		21.6 (83/385)		14.3 (5/35)		16.7 (3/18)	
Dust exposure, n (%)		0.03		0.20		0.19		0.62
No exposure	10.7 (55/512)		12.5 (83/664)		7.3 (104/1418)		6.8 (157/2298)	
Occupational or home exposure	11.6 (109/936)		15.2 (135/887)		8.3 (218/2639)		7.5 (210/2789)	
Occupational and home exposure	16.0 (75/468)		12.0 (33/275)		9.2 (123/1330)		7.4 (61/825)	
Drinking, n (%)		0.47		0.02		0.01		0.18
Never	13.5 (192/1427)		16.5 (72/437)		8.1 (450/5577)		8.0 (147/1847)	
Former	13.7 (16/117)		20.3 (15/74)		16.2 (12/74)		6.7 (11/163)	
Current	11.7 (99/846)		12.4 (157/1270)		10.0 (68/683)		6.5 (174/2667)	
BMI group, n (%)		<0.001		<0.001		<0.001		<0.001
Underweight	23.0 (28/122)		28.4 (31/109)		16.0 (41/257)		14.2 (34/240)	
Normal	15.4 (191/1244)		16.7 (179/1069)		9.2 (293/3185)		8.4 (260/3102)	
Overweight	9.1 (77/843)		9.6 (72/747)		6.3 (143/2253)		5.9 (131/2232)	
Obesity	6.3 (12/190)		8.9 (15/169)		8.1 (53/655)		5.7 (41/717)	
Self-reported respiratory symptoms, n (%)		<0.001		<0.001		<0.001		<0.001
No symptom	11.7 (238/2042)		11.4 (197/1728)		7.8 (433/5536)		6.5 (362/5551)	
One symptom	19.1 (49/256)		23.9 (58/243)		12.0 (71/592)		13.3 (77/580)	
More than one symptom	34.5 (19/55)		38.1 (40/105)		17.3 (17/98)		22.1 (25/113)	
History of diseases								
Asthma, n (%)		<0.001		<0.001		<0.001		<0.001
No	12.1 (285/2354)		13.7 (283/2069)		7.8 (490/6261)		7.0 (434/6225)	
Yes	50.0 (23/46)		55.6 (15/27)		41.4 (41/99)		45.9 (32/74)	
Hypertension, n (%)		0.67		0.56		0.37		0.36
No	13.1 (172/1309)		13.8 (160/1161)		8.6 (317/3674)		7.6 (302/3956)	
Yes	12.5 (136/1090)		14.8 (138/934)		8.0 (214/2686)		7.0 (163/2336)	
DM, n (%)		0.25		0.41		0.75		0.61
No	13.1 (276/2103)		14.4 (266/1852)		8.4 (462/5505)		7.5 (421/5638)	
Yes	10.5 (31/294)		12.1 (28/231)		8.0 (68/851)		6.8 (43/631)	

Abbreviations: AO, Airflow obstruction; BMI, body mass index; DM, Diabetes mellitus.
Airflow obstruction: Forced expiratory volume in 1 s/forced vital capacity ratio < lower limits of normal.
Dust exposure: occupational dust exposure and biomass cooking fuel exposure.
Biomass cooking fuel: wood, charcoal and coal.
BMI group: Underweight: BMI<18.5 Normal: 18.5 ≤BMI < 24 kg/m^2 Overweight: 24 ≤BMI < 28 kg/m^2 Obesity: BMI ≥28 kg/m^2
Self-reported respiratory symptoms: presence of cough, phlegm, wheezing for three months per year, and/or dyspnea.
Dyspnea: the British modified Medical Research Council (mMRC) scale ≥2.
Hypertension: systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or self-reported use of antihypertensive medication.
DM: fasting glucose ≥7.0 mmol/L and/or self-reported DM.

than the prediction model for LLN defined AO (Table Appendix 6, Appendix 7 and Appendix 8). When using the LLN according to equation developed by Ip, the results were similar (Appendix table 9).

15. Discussion

We developed and validated user-friendly diagnostic prediction models in men and women respectively, with good performances based on readily accessible data from a large population cohort of older Chinese. Age, smoking status, drinking status, BMI, presence of respiratory symptoms, diagnosed asthma were incorporated in this prediction model, with 13% and 7% denoting the cut-off point for high risk in men and women, respectively. The model in men performed better than the model in women. And the model for LLN defined AO performed less well than the fixed ratio defined AO model. Nevertheless, the slight difference between these two models is acceptable.

16. Strengths

This is the first study to develop a COPD diagnostic model in a Chinese population, using data from a large population-based cohort. Compared to Western populations, the distribution of risk factors and

Table 3
Multivariable analysis of the development and validation samples for estimation of odds ratio (95% confidence interval) of the final prediction model (combined cohort) for airflow obstruction.

Variables	Men			Women		
	Development sample (n = 2402)	Validation sample (n = 2096)	Combined sample (n = 4496)	Development sample (n = 6360)	Validation sample (n = 6299)	Combined sample (n = 12659)
Age, per 10 years	1.98 (1.60–2.45)[e]	1.31 (1.14–1.50)[e]	1.48 (1.34–1.62)[d]	1.33 (1.17–1.53)[e]	1.20 (1.06–1.36)[d]	1.26 (1.15–1.38)[e]
Self-reported respiratory symptoms						
No symptom	1.00	1.00	1.00	1.00	1.00	1.00
One symptom	1.54 (1.06–2.25)[c]	2.17 (1.53–3.08)[e]	1.85 (1.44–2.39)[e]	1.43 (1.08–1.89)[c]	2.17 (1.66–2.84)[e]	1.75 (1.44–2.12)[e]
More than one symptom	2.59 (1.38–4.87)[d]	3.41 (2.18–5.35)[e]	3.14 (2.18–4.51)[e]	1.55 (0.87–2.78)	2.62 (1.55–4.43)[e]	2.07 (1.41–3.05)[e]
Smoking						
Never	1.00	1.00	1.00	1.00	1.00	1.00
Former	2.57 (1.84–3.60)[e]	2.54 (1.77–3.65)[e]	2.52 (1.98–3.22)[e]	2.13 (1.29–3.52)[d]	2.27 (1.24–4.16)[d]	2.26 (1.54–3.32)[e]
Current (0–29 pack-years)	2.51 (1.64–3.84)[e]	1.89 (1.25–2.85)[d]	2.17 (1.62–2.92)[e]	1.89 (1.09–3.27)[c]	2.93 (1.61–5.32)[e]	2.33 (1.56–3.49)[e]
Current (≥30pack-years)	3.38 (2.30–4.96)[e]	3.21 (2.19–4.70)[e]	3.25 (2.49–4.26)[e]	1.51 (0.57–4.02)	1.53 (0.38–6.09)	1.55 (0.70–3.43)
BMI group (RCS, 4 knots)						
Spline 1	1.00	1.00	1.00	1.00	1.00	1.00
Spline 2	0.96 (0.85–1.10)	0.85 (0.75–0.97)[c]	0.90 (0.83–0.99)[c]	0.89 (0.82–0.97)[c]	0.90 (0.82–0.99)[c]	0.90 (0.84–0.95)[e]
Spline 3	0.73 (0.48–1.11)	1.03 (0.67–1.59)	0.88 (1.65–1.18)	0.96 (0.71–1.31)	0.91 (0.64–1.29)	0.94 (0.74–1.18)
Spline 4	3.47 (0.54–22.23)	1.10 (0.19–6.37)	1.86 (0.52–6.67)	1.62 (0.51–5.10)	1.85 (0.54–6.41)	1.74 (0.76–4.00)
Drinking, n (%)						
Never	1.00	1.00	1.00	1.00	1.00	1.00
Former	0.82 (0.46–1.47)	0.96 (0.52–1.78)	0.94 (0.62–1.42)	1.80 (0.94–3.46)	0.81 (0.46–1.40)	1.12 (0.73–1.71)
Current	0.76 (0.58–0.99)[c]	0.70 (0.52–0.94)[c]	0.78 (0.64–0.94)[d]	1.29 (0.98–1.70)	0.90 (0.73–1.09)	0.97 (0.83–1.12)
Dignosed asthma	5.64 (2.89–11.00)[e]	6.47 (2.77–15.12)[e]	5.43 (3.24–9.12)[e]	7.46 (4.85–11.49)[e]	8.22 (4.96–13.63)[e]	7.69 (5.55–10.66)[e]
Model performance						
Discrimination						
AUC apparent[a]	0.735 (0.726–0.745)	0.730 (0.719–0.740)	0.739 (0.722–0.736)	0.634 (0.625–0.642)	0.646 (0.637–0.655)	0.636 (0.630–0.642)
AUC validated	0.719 (0.717–0.721)[f]	0.718 (0.685–0.751)[b]	0.723 (0.721–0.725)[f]	0.616 (0.613–0.618)[f]	0.625 (0.621–0.631)[b]	0.631 (0.629–0.633)[f]
Calibration						
Calibration-in-the-large	−0.090£	−0.017[b]	−0.051[f]	−0.165[f]	−0.157[b]	−0.055[f]
Calibration slope	0.945£	0.878[b]	0.969[f]	0.928[f]	1.016[b]	0.975[f]

Abbreviations: BMI, body mass index; AUC, area under the receiver operating characteristic.
Airflow obstruction: Forced expiratory volume in 1 s/forced vital capacity ratio < lower limits of normal.
Splines for BMI in model were based on men and women respectively. Knots for BMI in men were at 18.4, 22.4, 24.6, and 28.9 kg/m^2, and that in women were at 18.8, 22.5, 24.9 and 29.5 kg/m^2.
Self-reported respiratory symptoms: cough, phlegm, wheezing for three months per year, and/or dyspnea.
Dyspnea: the British modified Medical Research Council (mMRC) scale ≥2.
[a] Performance was evaluated on the data to derive the final model.
[f] Estimated by internal validation (bootstrap method).
[b] Estimated by applying the model from the development data set in the validation data set (external validation).
[c] P < 0.05.
[d] P < 0.01.
[e] P < 0.001.

the prevalence and characteristics of undiagnosed COPD differs in low and middle income countries like China. Overfitting, a key problem in developing prediction models, was cautiously avoided in our study with the big sample size, very large number of individuals with AO (n = 1603) and careful prediction modelling strategy (stacked method, bootstrapping internal validation and external validation procedures). We further developed models in men and women separately considering the remarkably different prevalence of AO between them, and reversed regression coefficients of sex in the modle. The stratified analysis by sex might enhance the efficience of the models.

17. Limitations

Our study had several limitations. First, the participants with missing spirometry data were not included. However, as reported in our previous manuscript [15] and based on the analysis on the present study sample (Appendix table 1), the characteristics of participants with valid and invalid spirometry were not substantially different. Second, we used AO, as the outcome for our prediction model. AO may not be the same as a clinical definition for COPD. Furthermore the definition of AO was based on pre-bronchodilator spirometry. Third, some predictors were not included as candidate variables in our study, such as salbutamol or antibiotic prescriptions [12], which might indicate asthma or respiratory infection. We also did not include the same measure of socio-economic status as that used in existing diagnostic models. The Carstairs Index of Deprivation [11], used in former COPD prediction models is not suitable for developing country settings. However, we found the analogous measurements (educational level and occupation) were excluded in the model development. Fourth, the external validation sample was from a later time period (narrow validation), and we did not have a geographic or broad validation sample. However, the different population characteristics in the development and validation samples suggests the data sets could be considered as different samples, which is appropriate for validation. Fifth, The AUC of the model in men was satisfactory (0.718). In women, the AUC was rather low (0.625), indicating that it was more difficult to separate low from high risk women. The lower AO prevalence in women and other undiscovered predictors of AO in women might have led to the lower AUC. A lower AUC means worse discrimination, but the calibration performance of the model in women was as acceptable as that in men. Sixth, we developed updated model based on a combined sample with slightly changed effects and algorithms. Indeed, further validation is needed before

Table 4
Final predictors in updated prediction model for airflow obstruction in men and women.

Predictors	Men			Woman		
	Regression coefficient β	95% CI	P-value	Regression coefficient β	95% CI	P-value
Predictors						
Age, per 10 years	0.466	0.033 to 0.060	<0.001	0.231	0.140 to 0.322	<0.001
Self-reported respiratory symptoms			<0.001			0.006
No symptom	reference			reference		
One symptom	0.616	0.362 to 0.870		0.558	0.365 to 0.751	
More than one symptom	1.144	0.781 to 1.507		0.729	0.344 to 1.114	
Smoking			<0.001			0.001
Never	reference			reference		
Former	0.925	0.681 to 1.170		0.816	0.432 to 1.200	
Current (0–29 pack-years)	0.776	0.480 to 1.072		0.846	0.444 to 1.249	
Current (≥30pack-years)	1.179	0.910 to 1.448		0.440	−0.352 to 1.232	
BMI group (RCS, 4 knots)			<0.001			<0.001
Spline 1	reference			reference		
Spline 2	−0.101	−0.191 to −0.011		−0.109	−0.171 to −0.046	
Spline 3	−0.132	−0.431 to 0.167		−0.066	−0.296 to 0.164	
Spline 4	−0.618	−0.660 to −1.897		0.552	−0.281 to 1.385	
Drinking			0.06			0.03
Never	reference			reference		
Former	−0.066	−0.482 to 0.349		0.113	−0.309 to 0.537	
Current	−0.253	−0.442 to −0.064		−0.035	−0.184 to 0.113	
Dignosed asthma	1.692	1.174 to 2.210	<0.001	2.040	1.713 to 2.367	<0.001
Constant	−3.181	−5.246 to −1.117	<0.001	−1.519	−2.936 to −0.102	<0.001

Abbreviations: BMI, body mass index; CI, confidence interval.
Splines for BMI in model were based on men and women respectively. Knots for BMI in men were at 18.4, 22.4, 24.6, and 28.9 kg/m^2, and that in women were at 18.8, 22.5, 24.9 and 29.5 kg/m^2.
Self-reported respiratory symptoms: presence of cough, phlegm, wheezing for three months per year, and/or dyspnea.
Dyspnea: the British modified Medical Research Council (mMRC) scale ≥2.
Airflow obstruction: Forced expiratory volume in 1 s/forced vital capacity ratio < lower limits of normal.
Predicted probability of airflow obstruction in men = $\exp^{lp}/(1+\exp^{lp})$, lp = 0.466*age (per 10 year)+0*(never smoker)+0.925*(former smoker)+0.776*(Current smoker (0–29 pack-years))+1.179*(Current smoker ((≥30 pack-years))+0*(BMI spline 1)-0.101*(BMI spline 2)-0.132*(BMI spline 3)-0.618*(BMI spline 4)+0*(never drinker)-0.066*(former drinker)-0.253*(Current drinker) +0*(no respiratory symptom)+0.616*(one respiratory symptom)+1.144*(more than one respiratory symptom)+1.692*(diagnosed asthma)-3.181.
Predicted probability of airflow obstruction in women = $\exp^{lp}/(1+\exp^{lp})$, lp = 0.231*age (per 10 year)+0*(never smoker)+0.816*(former smoker)+0.846*(Current smoker (0–29 pack-years))+0.440*(Current smoker ((≥30 pack-years))+0*(BMI spline 1)-0.109*(BMI spline 2)-0.066*(BMI spline 3)+0.552*(BMI spline 4)+ 0*(never drinker)+0.113*(former drinker)-0.035*(Current drinker) +0*(no respiratory symptom)+0.558*(one respiratory symptom)+0.729*(more than one respiratory symptom)+2.040*(diagnosed asthma)-1.519.

applying the prediction model in a specific context, e.g. for screening purposes.

18. Interpretation

Our model for predicting the risk of AO included demographic and socioeconomic data and symptom information from a large population sample. Risk factors for COPD were reported in many previous manuscripts [2], but only a few studies integrated these factors into an easy-to-use prediction model. The predictors included in previous prediction models were inconsistent. Most of the studies failed to report detailed essential information of study design and characteristics of participants, and model development, model specification and model performance were also not presented comprehensively. Similar to previous models from Haroon [12] and Kotz [11], we found age, smoking status, respiratory symptoms and diagnosed asthma predicted higher risks of AO. However, drinking status and lower BMI were additional predictors. We developed user-friendly prediction models for AO with satisfactory performances in Chinese men and women respectively, which have been externally validated and are ready to use by clinicians and patients.

19. Implications

Although external temporal validation in GBCS phase 3 showed good performance, further validation in different settings or different participants are recommended. Spirometry is promoted for regular health screening in China, but screening spirometry in the general population is not advocated by GOLD. Meanwhile, the application of our model to relatively healthy populations would be of value as a first step to improve the efficiency of spirometry for active case finding.

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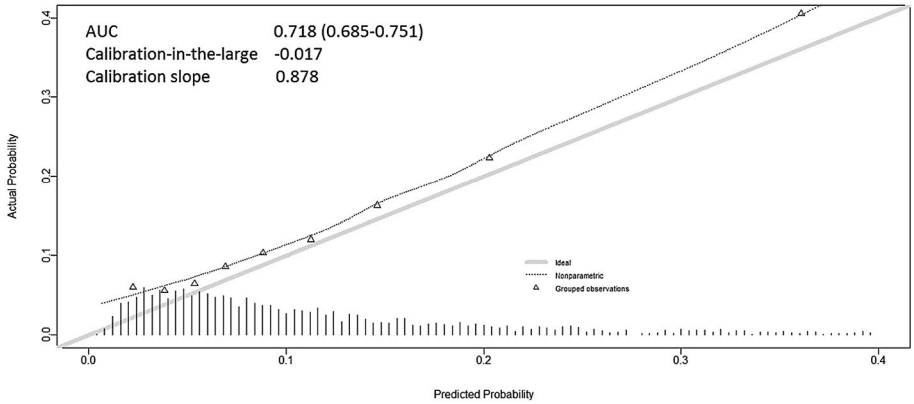
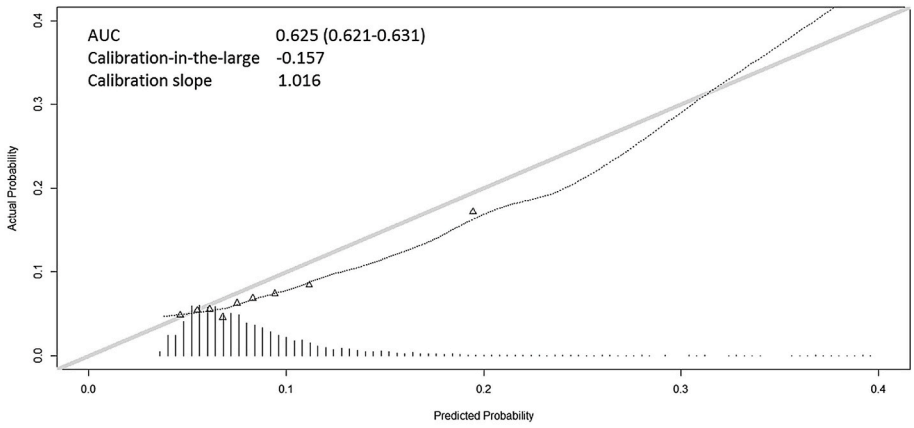
Abbreviations: GBCS, Guangzhou Biobank Cohort Study; BMI, body mass index; mMRC, the British modified Medical Research Council; AO, airflow obstruction; w/o, withoutAirflow obstruction: Forced expiratory volume in 1 s/forced vital capacity ratio < lower limits of normal.

CRediT authorship contribution statement

Jing Pan: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - review & editing. **Peymane Adab:** Conceptualization, Investigation, Project administration, Supervision, Validation, Visualization, Writing - review & editing. **K.K. Cheng:** Conceptualization, Project administration, Resources,



A. Validation plot in men



B. Validation plot in women

Fig. 3. Validation plot for the developed prediction model applied in the sample from GBCS phase 3 (external validation, n = 2096 in men and n = 6299 in women). Calibration-in-the-large calculated as the logistic regression model intercept given that the calibration slope equals 1; Calibration slope in a logistic regression model with the linear predictor as the sole predictor; AUC (area under ROC curve) indicating discriminative ability. Tick marks represent deciles of subjects grouped by similar predicted risk. The distribution of subjects with airflow obstruction is indicated with spikes at the bottom of the graph.
Airflow obstruction: Forced expiratory volume in 1 s
/
forced vital capacity ratio
<
lower limits of normal.

Supervision, Writing - review & editing. **Chao Qiang Jiang:** Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Supervision, Validation, Writing - review & editing. **Wei Sen Zhang:** Data curation, Funding acquisition. **Feng Zhu:** Data curation, Project administration, Writing - review & editing. **Ya Li Jin:** Data curation, Project administration. **G. Neil Thomas:** Project administration, Supervision. **Ewout W. Steyerberg:** Methodology, Resources, Supervision, Validation, Visualization, Writing - review & editing. **Tai Hing Lam:** Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Supervision, Validation, Writing - review & editing.

Declaration of competing interest

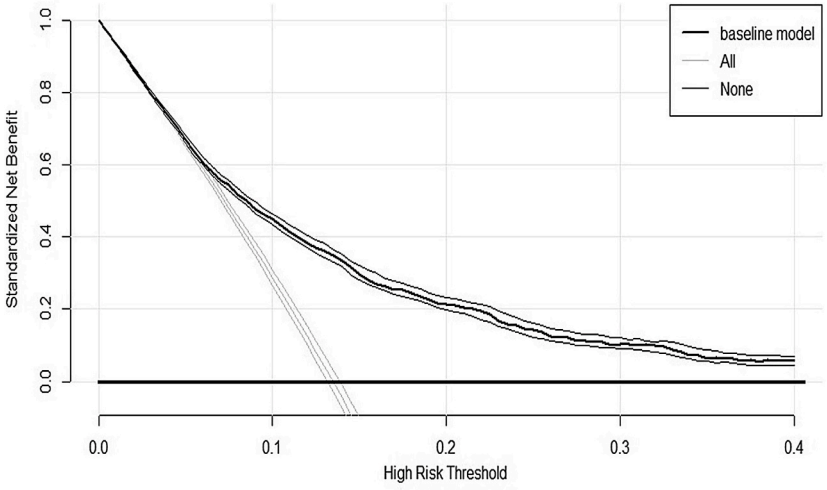
We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled, "**Development and validation of a prediction model for airflow obstruction in older Chinese: Guangzhou Biobank Cohort Study**".

Appendix

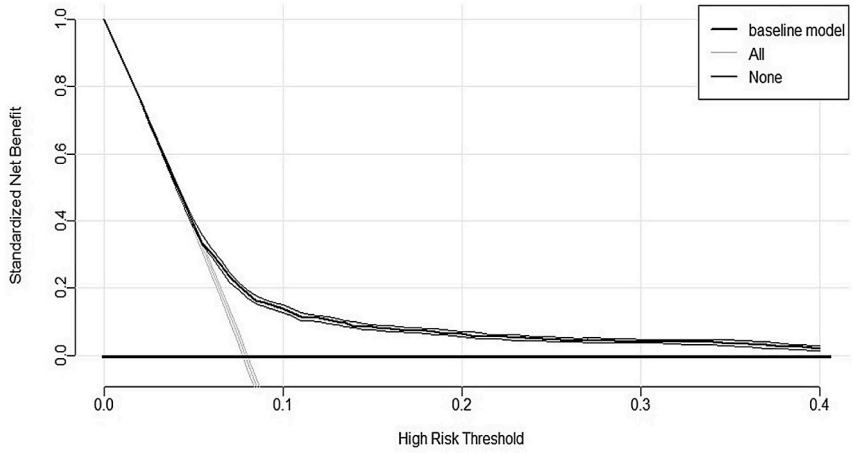
Appendix table 1
Characteristics of participants with and without valid spirometry measurement

	GBCS participants without valid spirometry measurement	GBCS participants with valid spirometry measurement	P value
Number	13273	17157	
Median Age (IQR), year	62.5 (56.9–68.0)	60.5 (55.3–67.0)	<0.001
Male, n (%)	3932 (29.6)	4498 (26.2)	<0.001
Education, n (%)			<0.001
≤Primary	6033 (45.5)	7013 (40.9)	
Middle school	6010 (45.3)	8634 (50.4)	
≥College	1216 (9.2)	1502 (8.8)	
Occupation, n (%)			<0.001
Manual	7512 (62.5)	7427 (46.8)	
Non-manual	3787 (31.5)	6054 (38.2)	

(*continued on next page*)



A. Decision curve in men



B. Decision curve in women

Fig. 4. Decision curves with 95% confidence interval for the final prediction models applied in combined sample. Solid line: Assume no participants are tested, net benefit is zero (no true-positive and no false-positive classifications); Grey line: assume all participants are tested; Black lines: participants are tested if predictions exceed a threshold, with the prediction model. The graph gives the expected net benefit per participants relative to no test in any participants ('Test none')
Airflow obstruction: Forced expiratory volume in 1 s
/
forced vital capacity ratio
<
lower limits of normalStandard
NB: NB/AO prevalence.

Appendix table 1 (*continued*)

	GBCS participants without valid spirometry measurement	GBCS participants with valid spirometry measurement	P value
Others	719 (6.0)	2374 (15.0)	
Smoking, n (%)			0.02
Never smoker	10598 (80.1)	13890 (81.3)	
Former smoker	1292 (9.8)	1491 (8.7)	
Current smoker (0–29 pack-years)	684 (5.2)	865 (5.1)	
Current smoker (≥30 pack-years)	662 (5.0)	845 (4.9)	
Dust exposure, n (%)			<0.001
No exposure	3037 (27.4)	4894 (32.5)	
Occupational or home exposure	5299 (47.8)	7252 (48.2)	
Occupational and home exposure	2757 (24.9)	2898 (19.3)	
Drinking, n (%)			<0.001
Never	9671 (75.2)	9291 (61.2)	
Former	296 (2.3)	428 (2.8)	
Current	2889 (22.5)	5466 (36.0)	
Median BMI (IQR), kg/m^2	23.6 (21.5–25.8)	23.6 (21.6–25.9)	0.09
BMI group, n (%)			0.02
Underweight	657 (5.0)	728 (4.3)	
Normal	6625 (50.2)	8600 (50.2)	
Overweight	4636 (35.1)	6075 (35.5)	
Obesity	1276 (9.7)	1731 (10.1)	
Self-reported respiratory symptoms, n (%)			0.86
No symptom	11457 (88.1)	14934 (88.0)	
One symptom	1254 (9.7)	1668 (9.8)	
More than one symptom	288 (2.2)	371 (2.2)	
History of diseases			
Asthma, n (%)	153 (1.2)	245 (1.4)	0.04

(*continued on next page*)

Appendix table 1 (*continued*)

	GBCS participants without valid spirometry measurement	GBCS participants with valid spirometry measurement	P value
Hypertension, n (%)	5846 (44.2)	7047 (41.1)	<0.001
DM, n (%)	1761 (13.3)	2008 (11.7)	<0.001

Abbreviations: IQR, interquartile range; BMI, body mass index; DM, Diabetes mellitus.
Dust exposure: occupational dust exposure and biomass cooking fuel exposure.
Biomass cooking fuel: wood, charcoal and coal.
BMI group: Underweight: BMI<18.5 Normal: 18.5 ≤BMI < 24 kg/m2 Overweight: 24 ≤BMI < 28 kg/m2 Obesity: BMI ≥28 kg/m2.
Self-reported respiratory symptoms: cough, phlegm, wheezing for three months per year, and/or dyspnea.
Dyspnea: the British modified Medical Research Council (mMRC) scale ≥2.
Hypertension: systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or self-reported use of antihypertensive medication.
DM: fasting glucose ≥7.0 mmol/L and/or self-reported DM.
P values based on Pearson chi-squared test for categorical variables, and nonparametric equality-of-medians for continuous variables.

Appendix table 2
Sensitivity and specificity of each cut-off point of the final prediction model for airflow obstruction in men and women

Sex groups	Cut-off point (%)	Sensitivity (%)	Specificity (%)	Youden' s index
Men	1	100	0	0
	2	99	1	0
	3	99	5	4
	4	97	12	9
	5	95	18	13
	6	91	26	17
	7	88	33	21
	8	86	39	25
	9	82	46	28
	10	80	51	31
	11	75	57	32
	12	72	61	33
	13	**69**	**66**	**35***
	14	65	70	35
	15	60	73	33
	16	56	76	32
	17	53	79	32
	18	50	82	32
	19	47	84	31
	20	45	85	30
Women	1	100	0	0
	2	100	0	0
	3	100	0	0
	4	99	2	1
	5	87	22	9
	6	74	42	16
	7	**60**	**58**	**18***
	8	48	71	19
	9	40	79	19
	10	33	85	18
	11	27	89	16
	12	24	92	16
	13	20	94	14
	14	18	95	13
	15	16	96	12
	16	15	97	12
	17	14	97	11
	18	13	98	11
	19	12	98	10
	20	12	98	10

*: In men, cut-off point of 13% with the highest Youden's index and satisfactory sensitivity was proposed as the threshold for the decision for conducting spirometry. In women, cut-off point of 7% with satisfactory sensitivity and second highest Youden's index was proposed as the threshold for the decision for conducting spirometry.
Youden's index = sensitivity + specificity-1.
Airflow obstruction: Forced expiratory volume in 1 s/forced vital capacity ratio < lower limits of normal.

Appendix table 3
Net benefit of test all, test none, test based on final prediction model for airflow obstruction in men and women

Sex groups	Probability threshold	NB of test all	NB of test none	NB of test based on prediction model	Standard NB of test based on model	Spirometry avoided per 100 patients	Increase in NB from using model
Men	0.01	0.13	0.00	0.13	0.94	0.02	0.00
	0.02	0.12	0.00	0.12	0.86	−3.54	0.00
	0.03	0.11	0.00	0.11	0.80	−1.69	0.00

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Appendix table 3 (*continued*)

Sex groups	Probability threshold	NB of test all	NB of test none	NB of test based on prediction model	Standard NB of test based on model	Spirometry avoided per 100 patients	Increase in NB from using model
	0.04	0.10	0.00	0.10	0.74	1.02	0.00
	0.05	0.09	0.00	0.09	0.67	2.55	0.00
	0.06	0.08	0.00	0.08	0.61	3.38	0.00
	0.07	0.07	0.00	0.07	0.56	7.10	0.01
	0.08	0.06	0.00	0.07	0.52	11.88	0.01
	0.09	0.05	0.00	0.06	0.48	15.40	0.02
	0.10	0.04	0.00	0.06	0.45	19.96	0.02
	0.11	0.03	0.00	0.06	0.41	22.48	0.03
	0.12	0.02	0.00	0.05	0.38	25.44	0.03
	0.13	**0.01**	**0.00**	**0.05**	**0.36**	**28.96**	**0.04**
	0.14	−0.01	0.00	0.04	0.33	31.23	0.05
	0.15	−0.02	0.00	0.04	0.30	32.74	0.06
	0.16	−0.03	0.00	0.04	0.27	34.80	0.07
	0.17	−0.04	0.00	0.03	0.25	37.51	0.08
	0.18	−0.06	0.00	0.03	0.24	40.10	0.09
	0.19	−0.07	0.00	0.03	0.23	42.13	0.10
	0.20	−0.08	0.00	0.03	0.21	44.13	0.11
	0.21	−0.10	0.00	0.03	0.20	46.12	0.12
	0.22	−0.11	0.00	0.03	0.19	48.04	0.14
	0.23	−0.12	0.00	0.02	0.17	48.96	0.15
	0.24	−0.14	0.00	0.02	0.16	50.47	0.16
	0.25	−0.15	0.00	0.02	0.14	51.92	0.17
	0.26	−0.17	0.00	0.02	0.13	52.99	0.19
	0.27	−0.19	0.00	0.02	0.12	54.47	0.20
	0.28	−0.20	0.00	0.02	0.11	55.74	0.22
	0.29	−0.22	0.00	0.01	0.11	57.15	0.23
	0.30	−0.24	0.00	0.01	0.10	58.36	0.25
Women	0.01	0.07	0.00	0.07	0.88	0.00	0.00
	0.02	0.06	0.00	0.06	0.76	0.00	0.00
	0.03	0.05	0.00	0.05	0.64	0.00	0.00
	0.04	0.04	0.00	0.04	0.51	−0.38	0.00
	0.05	0.03	0.00	0.03	0.39	0.62	0.00
	0.06	0.02	0.00	0.02	0.3	6.13	0.00
	0.07	**0.01**	**0.00**	**0.02**	**0.23**	**11.81**	**0.01**
	0.08	0.00	0.00	0.01	0.19	18.40	0.02
	0.09	−0.01	0.00	0.01	0.16	24.84	0.02
	0.10	−0.02	0.00	0.01	0.14	30.97	0.03
	0.11	−0.04	0.00	0.01	0.12	35.72	0.04
	0.12	−0.05	0.00	0.01	0.11	40.85	0.06
	0.13	−0.06	0.00	0.01	0.1	44.63	0.07
	0.14	−0.07	0.00	0.01	0.09	47.90	0.08
	0.15	−0.08	0.00	0.01	0.08	51.23	0.09
	0.16	−0.10	0.00	0.01	0.08	53.98	0.10
	0.17	−0.11	0.00	0.01	0.07	56.45	0.12
	0.18	−0.12	0.00	0.01	0.07	58.90	0.13
	0.19	−0.14	0.00	0.01	0.07	60.74	0.14
	0.20	−0.15	0.00	0.01	0.06	62.63	0.16
	0.21	−0.17	0.00	0.00	0.06	64.13	0.17
	0.22	−0.18	0.00	0.00	0.05	65.72	0.19
	0.23	−0.20	0.00	0.00	0.05	67.16	0.20
	0.24	−0.21	0.00	0.00	0.05	68.41	0.22
	0.25	−0.23	0.00	0.00	0.05	69.58	0.23
	0.26	−0.24	0.00	0.00	0.04	70.71	0.25
	0.27	−0.26	0.00	0.00	0.05	71.78	0.27
	0.28	−0.28	0.00	0.00	0.04	72.73	0.28
	0.29	−0.30	0.00	0.00	0.04	73.64	0.30
	0.30	−0.32	0.00	0.00	0.04	74.49	0.32

Abbreviations: NB: net benefit.

*: Suggested threshold for decision for spirometry.

Airflow obstruction: Forced expiratory volume in 1 s/forced vital capacity ratio < lower limits of normal.

Standard NB: NB/AO prevalence.

Appendix table 4

Prevalence of fixed ratio defined airflow obstruction in the development and validation sample

Characteristics	Men				Women			
	Prevalence of AO in the development sample (n = 2402)		Prevalence of AO in the validation sample (n = 2069)		Prevalence of AO in the development sample (n = 6360)		Prevalence of AO in the validation sample (n = 6299)	
	% (No./Total)	P value	% (No./Total)	P value	% (No./Total)	P value	% (No./Total)	P value
Total	15.6 (375/2402)		17.5 (367/2069)		7.2 (459/6360)		5.7 (361/6299)	

(*continued on next page*)

Appendix table 4 (*continued*)

Characteristics	Men				Women			
	Prevalence of AO in the development sample (n = 2402)		Prevalence of AO in the validation sample (n = 2069)		Prevalence of AO in the development sample (n = 6360)		Prevalence of AO in the validation sample (n = 6299)	
	% (No./Total)	P value	% (No./Total)	P value	% (No./Total)	P value	% (No./Total)	P value
Age group, n (%)		<0.001		<0.001		<0.001		<0.001
<60	5.3 (32/601)		8.5 (65/762)		4.1 (120/2906)		3.1 (121/3903)	
60–69.9	16.1 (203/1257)		18.4 (164/891)		8.5 (224/2625)		7.8 (128/1637)	
≥70	25.7 (140/544)		31.2 (138/443)		13.9 (115/829)		14.8 (112/759)	
Education, n (%)		0.005		<0.001		<0.001		<0.001
≤Primary	19.4 (136/701)		26.7 (159/596)		8.4 (269/3195)		8.9 (224/2521)	
Middle school	13.9 (176/1263)		14.2 (169/1188)		5.9 (166/2802)		3.4 (116/3381)	
≥College	14.4 (63/437)		12.5 (39/311)		6.4 (23/359)		5.3 (21/395)	
Occupation, n (%)		0.85		0.001		0.63		0.04
Manual	15.7 (171/1087)		22.5 (130/579)		7.6 (316/4173)		6.9 (109/1588)	
Non-manual	16.3 (158/967)		16.3 (158/967)		7.5 (89/1186)		5.0 (147/2934)	
Others	18.4 (9/49)		14.7 (76/516)		9.8 (13/133)		5.8 (98/1676)	
Smoking, n (%)		<0.001		<0.001		<0.001		<0.001
Never	9.1 (84/920)		9.7 (75/776)		6.7 (412/6105)		5.3 (320/6089)	
Former	19.9 (149/750)		23.2 (127/547)		20.2 (23/114)		22.5 (18/80)	
Current (0–29 pack-years)	17.6 (57/323)		17.4 (65/374)		19.4 (19/98)		20.0 (14/70)	
Current (≥30 pack-years)	20.9 (85/407)		25.2 (97/385)		14.3 (5/35)		22.2 (4/18)	
Dust exposure, n (%)		0.049		0.047		0.20		0.09
No exposure	13.8 (71/514)		14.3 (95/664)		6.3 (89/1418)		4.7 (109/2298)	
Occupational or home exposure	14.3 (134/937)		19.1 (169/887)		7.2 (190/2639)		5.8 (162/2789)	
Occupational and home exposure	18.8 (88/468)		17.8 (49/275)		8.0 (107/1330)		6.5 (54/825)	
Drinking, n (%)		0.92		0.002		0.008		0.15
Never	15.9 (227/1430)		21.1 (92/437)		7.0 (392/5577)		6.2 (115/1847)	
Former	15.4 (18/117)		25.7 (19/74)		16.2 (12/74)		4.9 (8/163)	
Current	15.2 (129/846)		15.0 (190/1270)		8.6 (54/683)		1.2 (131/2667)	
BMI group, n (%)		<0.001		<0.001		<0.001		<0.001
Underweight	28.7 (35/122)		32.1 (35/109)		17.1 (44/257)		12.5 (30/240)	
Normal	18.3 (228/1244)		19.9 (213/1069)		7.6 (241/3185)		6.3 (191/3102)	
Overweight	11.3 (95/843)		13.4 (100/747)		5.6 (126/2253)		4.8 (108/2232)	
Obesity	8.9 (17/190)		10.7 (18/169)		7.2 (47/655)		4.5 (32/717)	
Self-reported respiratory symptoms, n (%)		<0.001		<0.001		<0.001		<0.001
No symptom	14.3 (292/2045)		14.2 (246/1728)		6.6 (367/5536)		4.9 (270/5551)	
One symptom	23.4 (60/256)		28.4 (69/243)		11.0 (65/592)		11.0 (64/580)	
More than one symptom	38.2 (21/55)		46.7 (49/105)		18.4 (18/98)		22.1 (25/113)	
History of diseases								
Asthma, n (%)		<0.001		<0.001		<0.001		<0.001
No	15.0 (354/2357)		17.0 (351/2069)		6.7 (421/6261)		5.4 (334/6225)	
Yes	52.5 (21/45)		59.3 (16/27)		38.4 (38/99)		36.5 (27/74)	
Hypertension, n (%)		0.72		0.11		0.30		0.045
No	15.3 (201/1311)		16.3 (189/1161)		6.9 (254/3674)		5.3 (208/3956)	
Yes	15.7 (174/1091)		19.1 (178/934)		7.6 (205/2686)		6.5 (152/2336)	
DM, n (%)		0.67		0.78		0.31		0.95
No	15.7 (331/2105)		17.4 (323/1852)		7.1 (389/5505)		5.7 (322/5638)	
Yes	14.6 (43/295)		16.5 (38/231)		8.1 (69/851)		5.9 (37/631)	

Abbreviation: BMI, body mass index; DM, Diabetes mellitus.
Airflow obstruction: Forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio <0.70.
Dust exposure: occupational dust exposure and biomass cooking fuel exposure.
Biomass cooking fuel: wood, charcoal and coal.
BMI group: Underweight: BMI<18.5 Normal: 18.5 ≤BMI < 24 kg/m^2 Overweight: 24 ≤BMI < 28 kg/m^2 Obesity: BMI ≥28 kg/$m.^2$.
Self-reported respiratory symptoms: presence of cough, phlegm, wheezing for three months per year, and/or dyspnea.
Dyspnea: the British modified Medical Research Council (mMRC) scale ≥2.
Hypertension: systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or self-reported use of antihypertensive medication.
DM: fasting glucose ≥7.0 mmol/L and/or self-reported DM.

Appendix table 5
Multivariable analysis of the development and validation samples for estimation of odds ratio (95% confidence interval) of the final prediction model (combined cohort) for fixed ratio defined airflow obstruction

Variables	Men			Women		
	Development sample (n = 2402)	Validation sample (n = 2096)	Combined sample (n = 4498)	Development sample (n = 6360)	Validation sample (n = 6299)	Combined sample (n = 12659)
Age, per 10 years	2.86 (2.33–3.50)***	2.19 (1.86–2.59)***	2.44 (2.15–2.78)***	2.05 (1.77–2.37)***	2.21 (1.93–2.52)***	2.13 (1.93–2.35)***
Self-reported respiratory symptoms						
No symptom	1.00	1.00	1.00	1.00	1.00	1.00
One symptom	1.68 (1.18–2.38)**	2.08 (1.49–2.91)***	1.88 (1.48–2.39)***	1.51 (1.12–2.02)**	2.27 (1.68–3.07)***	1.82 (1.47–2.24)***
More than one symptom	2.59 (1.40–4.82)**	3.56 (2.28–5.54)***	3.27 (2.29–4.68)***	1.75 (0.98–3.14)	3.49 (2.01–6.05)***	2.46 (1.66–3.65)***

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Appendix table 5 (*continued*)

Variables	Men			Women		
	Development sample (n = 2402)	Validation sample (n = 2096)	Combined sample (n = 4498)	Development sample (n = 6360)	Validation sample (n = 6299)	Combined sample (n = 12659)
Smoking						
Never	1.00	1.00	1.00	1.00	1.00	1.00
Former	2.20 (1.63–2.98)***	2.55 (1.83–3.54)***	2.32 (1.86–2.89)***	2.20 (1.33–3.63)**	2.41 (1.36–4.28)**	2.35 (1.61–3.42)***
Current (0–29 pack-years)	2.40 (1.63–3.53)***	2.11 (1.44–3.10)***	2.22 (1.69–2.92)***	2.02 (1.17–3.49)*	2.77 (1.48–5.17)**	2.38 (1.58–3.59)***
Current (≥30pack-years)	2.91 (2.06–4.13)***	3.31 (2.32–4.73)***	3.07 (2.40–3.93)***	1.50 (0.55–4.07)	1.62 (0.43–6.03)	1.57 (0.71–3.47)
Drinking,						
Never				1.00	1.00	1.00
Former				1.96 (1.01–3.81)*	0.71 (0.37–1.35)	1.06 (0.66–1.68)
Current				1.23 (0.91–1.68)	0.91 (0.72–1.14)	0.93 (0.79–1.10)
BMI group (RCS, 4 knots)						
Spline 1	1.00	1.00	1.00	1.00	1.00	1.00
Spline 2	0.94 (0.83–1.06)	0.87 (0.77–0.99)*	0.91 (0.83–0.99)*	0.85 (0.78–0.93)***	0.87 (0.79.-0.97)**	0.86 (0.81–0.92)***
Spline 3	0.78 (0.53–1.14)	1.07 (0.71–1.62)	0.90 (0.68–1.20)	1.15 (0.83–1.60)	1.08 (0.72–1.61)	1.11 (0.87–1.43)
Spline 4	3.44 (0.65–18.23)	0.81 (0.15–4.34)	1.69 (0.52–5.47)	0.84 (0.24–2.86)	0.94 (0.22–3.94)	0.90 (0.36–2.26)
Dignosed asthma	3.53 (1.80–6.94)***	5.68 (2.35–13.73)***	3.90 (2.30–6.60)***	7.66 (4.87–12.06)***	8.49 (4.88–14.77)***	7.92 (5.59–11.23)***
Model performance						
Discrimination						
AUC apparent$	0.751 (0.743–0.759)	0.762 (0.753–0.770)	0.753 (0.747–0.759)	0.701 (0.693–0.709)	0.742 (0.733–0.751)	0.721 (0.715–0.727)
AUC validated	0.739 (0.736–0.743)£	0.755 (0.754–0.756) ¶	0.750 (0.748–0.752) £	0.689 (0.686–0.690)£	0.733 (0.730–0.736)¶	0.718 (0.716–0.719)£
Calibration						
Calibration-in-the-large	−0.089£	0.008¶	−0.027£	−0.106£	0.021¶	−0.038£
Calibration slope	0.939£	0.912¶	0.981£	0.955£	1.098¶	0.984£

Abbreviations: BMI, body mass index; AUC, area under the receiver operating characteristic.
Splines for BMI in model is based on men and women respectively. Knots for BMI in men were at 18.4, 22.4, 24.6, and 28.9 kg/m^2, and that in women were at 18.8, 22.5, 24.9 and 29.5 kg/m.^{2}.
Self-reported respiratory symptoms: cough, phlegm, wheezing for three months per year, and/or dyspnea.
Dyspnea: the British modified Medical Research Council (mMRC) scale ≥2.
Airflow obstruction: Forced expiratory volume in 1 s/forced vital capacity ratio <0.70.
$Performance was evaluated on the data to derive the final model.
£ Estimated by internal validation (bootstrap method).
¶Estimated by applying the model from the development data set in the validation data set (external validation).
*: P < 0.05.
**: P < 0.01.
***: P < 0.001.

Appendix table 6
Final predictors in updated prediction model for fixed ratio defined airflow obstruction in men and women

Predictors	Men			Women		
	Regression coefficient β	95% CI	P-value	Regression coefficient β	95% CI	P-value
Predictors						
Age, per 10 years	0.893	0.764 to 1.022	<0.001	0.755	0.657 to 0.852	<0.001
Self-reported respiratory symptoms			<0.001			<0.001
No symptom	reference	reference		reference		
One symptom	0.632	0.391 to 0.872		0.598	0.387 to 0.809	
More than one symptom	1.186	0.830 to 1.542		0.900	0.504 to 1.295	
Smoking			<0.001			<0.001
Never	reference	reference		reference		
Former	0.841	0.620 to 1.063		0.853	0.476 to 1.231	
Current (0–29 pack-years)	0.799	0.527 to 1.071		0.867	0.456 to 1.278	
Current (≥30pack-years)	1.122	0.874 to 1.370		0.454	−0.337 to 1.245	
Drinking,						0.44
Never				reference		
Former				0.056	−0.408 to 0.521	
Current				−0.072	−0.241 to 0.098	
BMI group (RCS, 4 knots)			<0.001			<0.001
Spline 1	reference	reference		reference		
Spline 2	−0.096	−0.182 to −0.010		−0.146	−0.212 to −0.080	
Spline 3	−0.101	−0.380 to 0.179		0.109	−0.142 to 0.360	
Spline 4	0.527	−0.646 to 1.699		−0.111	−1.035 to 0.814	
Dignosed asthma	1.361	0.835 to 1.887	<0.001	2.070	1.721 to 2.419	<0.001
Constant	−5.969	−7.949 to −3.998	<0.001	−4.331	−5.836 to −2.825	<0.001

Abbreviations: BMI, body mass index; CI, confidence interval.
Splines for BMI in model is based on men and women respectively. Knots for BMI in men were at 18.4, 22.4, 24.6, and 28.9 kg/m^2, and that in women were at 18.8, 22.5, 24.9 and 29.5 kg/m.^{2}.
Self-reported respiratory symptoms: presence of cough, phlegm, wheezing for three months per year, and/or dyspnea.

Dyspnea: the British modified Medical Research Council (mMRC) scale ≥2.
Airflow obstruction: Forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio <0.70.
Predicted probability of airflow obstruction in men = explp/(1 + exp^{lp}), lp = 0.893*age (per 10 year)+0*(never smoker)+0.841*(former smoker)+0.799*(Current smoker (0–29 pack-years))+1.122*(Current smoker ((≥30 pack-years))+0*(BMI spline 1)-0.096*(BMI spline 2)-0.101*(BMI spline 3)+0.527*(BMI spline 4)+0*(no respiratory symptom)+0.632*(one respiratory symptom)+1.186*(more than one respiratory symptom)+1.361*(diagnosed asthma)-5.969.
Predicted probability of airflow obstruction in women = explp/(1 + exp^{lp}), lp = 0.755*age(per 10 year)+0*(never smoker)+0.853*(former smoker)+0.867*(Current smoker (0–29 pack-years))+0.454*(Current smoker ((≥30 pack-years))+0*(BMI spline 1)-0.146*(BMI spline 2)+0.109*(BMI spline 3)-0.111*(BMI spline 4)+ 0*(never drinker)+0.056*(former drinker)-0.072*(Current drinker) +0*(no respiratory symptom)+0.598*(one respiratory symptom)+0.900*(more than one respiratory symptom)+2.070*(diagnosed asthma)-4.331.

Appendix table 7
Sensitivity and specificity of each cut-off point of the final prediction model for fixed ratio defined airflow obstruction in men and women

Sex groups	Cut-off point (%)	Sensitivity (%)	Specificity (%)	Youden' s index
Men	1	100	0	0
	2	100	1	1
	3	99	5	4
	4	98	10	9
	5	97	16	13
	6	95	22	17
	7	93	28	20
	8	91	34	25
	9	89	40	29
	10	86	45	31
	11	83	51	34
	12	**81**	**55**	**35***
	13	77	58	35
	14	75	62	37
	15	72	66	37
	16	69	68	37
	17	66	71	38
	18	65	74	38
	19	62	76	38
	20	60	78	38
Women	1	100	0	0
	2	99	5	4
	3	92	27	18
	4	82	45	27
	5	73	58	31
	6	**65**	**67**	**32***
	7	57	75	31
	8	51	80	31
	9	46	84	30
	10	40	87	26
	11	36	89	25
	12	33	91	24
	13	30	92	23
	14	28	94	22
	15	26	95	21
	16	25	95	20
	17	23	96	19
	18	21	97	18
	19	19	97	16
	20	17	97	14

*: Cut-off point 12% in men and 6% in women with the highest Youden's index and satisfied sensitivity was proposed as the threshold for the decision for conducting spirometry.
Youden's index = sensitivity + specificity-1.
Airflow obstruction: Forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio <0.70.

Appendix table 8
Net benefit of test all, test none, test based on final prediction model for fixed ratio defined airflow obstruction in men and women

Sex groups	Probability threshold	NB of test all	NB of test none	NB of test based on prediction model	Standard NB of test based on model	Spirometry avoided per 100 patients	Increase in NB from using model
Men	0.01	0.16	0.00	0.16	0.95	0.02	0.00
	0.02	0.15	0.00	0.15	0.9	−0.14	0.00
	0.03	0.14	0.00	0.14	0.85	1.01	0.00
	0.04	0.13	0.00	0.13	0.79	1.95	0.00
	0.05	0.12	0.00	0.12	0.75	5.18	0.00
	0.06	0.11	0.00	0.12	0.7	5.65	0.00
	0.07	0.10	0.00	0.11	0.65	6.95	0.01
	0.08	0.09	0.00	0.10	0.62	10.91	0.01
	0.09	0.08	0.00	0.10	0.59	14.62	0.01
	0.10	0.07	0.00	0.09	0.55	17.13	0.02

(*continued on next page*)

Appendix table 8 (*continued*)

Sex groups	Probability threshold	NB of test all	NB of test none	NB of test based on prediction model	Standard NB of test based on model	Spirometry avoided per 100 patients	Increase in NB from using model
	0.11	0.06	0.00	0.09	0.52	19.76	0.02
	0.12*	**0.05**	**0.00**	**0.08**	**0.49**	**22.15**	**0.03**
	0.13	0.04	0.00	0.08	0.46	23.53	0.04
	0.14	0.03	0.00	0.07	0.44	26.54	0.04
	0.15	0.02	0.00	0.07	0.41	28.49	0.05
	0.16	0.01	0.00	0.06	0.39	30.29	0.06
	0.17	−0.01	0.00	0.06	0.37	32.52	0.07
	0.18	−0.02	0.00	0.06	0.36	35.06	0.08
	0.19	−0.03	0.00	0.06	0.34	36.99	0.09
	0.20	−0.04	0.00	0.05	0.32	38.35	0.10
	0.21	−0.06	0.00	0.05	0.3	39.89	0.11
	0.22	−0.07	0.00	0.04	0.27	40.94	0.12
	0.23	−0.08	0.00	0.04	0.26	42.61	0.13
	0.24	−0.10	0.00	0.04	0.25	44.56	0.14
	0.25	−0.11	0.00	0.04	0.23	45.55	0.15
	0.26	−0.13	0.00	0.04	0.23	47.28	0.17
	0.27	−0.14	0.00	0.03	0.2	47.92	0.18
	0.28	−0.16	0.00	0.03	0.19	49.01	0.19
	0.29	−0.18	0.00	0.03	0.18	50.39	0.21
	0.30	−0.19	0.00	0.03	0.16	51.31	0.22
Women	0.01	0.06	0.00	0.06	0.85	0.00	0.00
	0.02	0.05	0.00	0.05	0.71	0.69	0.00
	0.03	0.04	0.00	0.04	0.59	7.37	0.00
	0.04	0.03	0.00	0.03	0.49	14.03	0.01
	0.05	0.02	0.00	0.03	0.41	20.48	0.01
	0.06*	**0.01**	**0.00**	**0.02**	**0.35**	**27.39**	**0.02**
	0.07	−0.01	0.00	0.02	0.29	32.60	0.02
	0.08	−0.02	0.00	0.02	0.26	38.45	0.03
	0.09	−0.03	0.00	0.01	0.23	42.91	0.04
	0.10	−0.04	0.00	0.01	0.19	46.02	0.05
	0.11	−0.05	0.00	0.01	0.17	50.03	0.06
	0.12*	−0.06	0.00	0.01	0.16	53.40	0.07
	0.13	−0.07	0.00	0.01	0.14	56.16	0.08
	0.14	−0.09	0.00	0.01	0.13	58.98	0.10
	0.15	−0.10	0.00	0.01	0.12	61.33	0.11
	0.16	−0.11	0.00	0.01	0.12	63.57	0.12
	0.17	−0.13	0.00	0.01	0.11	65.33	0.13
	0.18	−0.14	0.00	0.01	0.11	67.21	0.15
	0.19	−0.15	0.00	0.01	0.09	68.29	0.16
	0.20	−0.17	0.00	0.01	0.08	69.65	0.17
	0.21	−0.18	0.00	0.00	0.07	70.89	0.19
	0.22	−0.20	0.00	0.00	0.06	72.04	0.20
	0.23	−0.21	0.00	0.00	0.06	73.21	0.22
	0.24	−0.23	0.00	0.00	0.06	74.25	0.23
	0.25	−0.25	0.00	0.00	0.06	75.20	0.25
	0.26	−0.26	0.00	0.00	0.06	76.15	0.27
	0.27	−0.28	0.00	0.00	0.06	77.02	0.28
	0.28	−0.30	0.00	0.00	0.06	77.81	0.30
	0.29	−0.32	0.00	0.00	0.05	78.48	0.32
	0.30	−0.34	0.00	0.00	0.05	79.18	0.34

Abbreviations: NB: net benefit.

*: Suggested threshold for decision for spirometry.

Airflow obstruction: Forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio <0.70.

Standard NB: NB/AO prevalence.

Appendix table 9

Multivariable analysis of the development and validation samples for estimation of odds ratio (95% confidence interval) of the final prediction model (combined cohort) for airflow obstruction

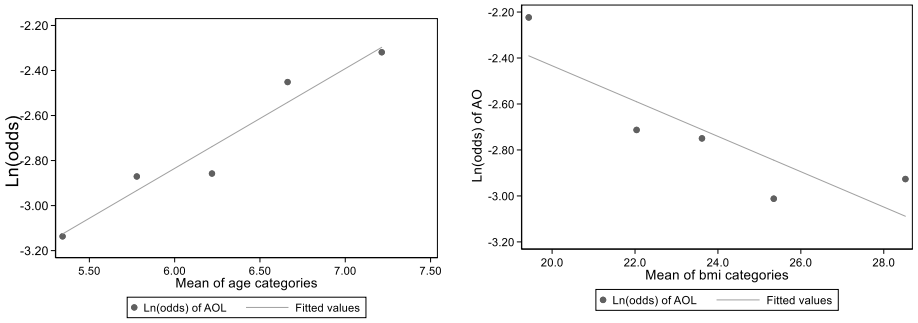
Variables	Men			Women		
	Development sample (n = 2402)	Validation sample (n = 2096)	Combined sample (n = 4496)	Development sample (n = 6360)	Validation sample (n = 6299)	Combined sample (n = 12659)
Age, per 10 years	2.23 (1.65–3.01)***	1.65 (1.31–2.08)***	1.86 (1.55–2.24)***	1.26 (1.07–1.48)**	1.09 (0.93–1.28)	1.18 (1.05–1.32)**
Education						
≤Primary				1.00	1.00	1.00
Middle school				0.83 (0.66–1.04)	0.64 (0.50–0.84)***	0.74 (0.62–0.88)***
≥College				0.67 (0.40–1.13)	1.18 (0.77–1.80)	0.94 (0.68–1.30)
Self-reported respiratory symptoms						
No symptom	1.00	1.00	1.00	1.00	1.00	1.00
One symptom	1.73 (1.05–2.84)*	2.517 (1.60–3.94)***	2.08 (1.50–2.90)***	1.59 (1.18–2.15)**	2.56 (1.91–3.44)***	1.99 (1.61–2.45)***
More than one symptom	3.76 (1.83–7.71)***	4.69 (2.78–7.91)***	4.45 (2.95–6.73)***	1.69 (0.91–3.15)	3.24 (1.87–5.62)***	2.44 (1.63–3.66)***

(*continued on next page*)

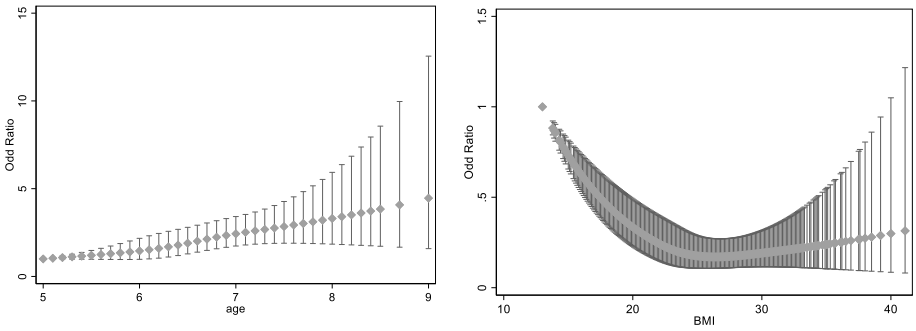
Appendix table 9 (*continued*)

Variables	Men			Women		
	Development sample (n = 2402)	Validation sample (n = 2096)	Combined sample (n = 4496)	Development sample (n = 6360)	Validation sample (n = 6299)	Combined sample (n = 12659)
Smoking						
Never	1.00	1.00	1.00	1.00	1.00	1.00
Former	2.75 (1.71–4.41)***	4.06 (2.417–6.85)***	3.25 (2.29–4.61)***	2.25 (1.31–3.86)**	2.10 (1.07–4.13)*	2.29 (1.50–3.47)***
Current (0–29 pack-years)	2.68 (1.49–4.84)**	2.93 (1.62–5.29)***	2.74 (1.81–4.14)***	2.01 (1.12–3.60)*	3.00 (1.55–5.81)**	2.40 (1.56–3.71)***
Current (≥30pack-years)	2.40 (1.36–4.23)**	3.45 (1.95–6.08)***	2.87 (1.93–4.26)***	1.42 (0.48–4.19)	1.83 (0.43–7.71)	1.58 (0.67–3.72)
BMI group (RCS, 4 knots)						
Spline 1	1.00	1.00	1.00	1.00	1.00	1.00
Spline 2	0.92 (0.77–1.08)	0.85 (0.73–0.99)*	0.88 (0.79–0.99)*	0.86 (0.78–0.94)**	0.89 (0.80–0.99)*	0.87 (0.81–0.94)***
Spline 3	0.82 (0.47–1.44)	0.84 (0.48–1.45)	0.84 (0.57–1.25)	1.12 (0.80–1.58)	0.87 (0.59–1.29)	1.00 (0.78–1.30)
Spline 4	2.90 (0.24–35.33)	3.00 (0.32–28.31)	2.79 (0.52–15.06)	0.95 (0.26–3.41)	2.39 (0.59–9.60)	1.43 (0.56–3.63)
Drinking, n (%)						
Never				1.00	1.00	1.00
Former				2.09 (1.06–4.14)*	0.93 (0.51–1.70)	1.19 (0.75–1.90)
Current				1.15 (0.83–1.58)	1.01 (0.80–1.27)	1.00 (0.84–1.18)
Diabetes mellitus	0.63 (0.33–1.21)	1.12 (0.62–2.01)	0.83 (0.54–1.27)			
Dignosed asthma	6.19 (2.94–13.00)***	10.40 (4.20–25.76)***	6.78 (3.87–11.88)***	8.48 (5.44–13.22)***	10.44 (6.19–17.60)***	9.13 (6.53–12.77)***
Model performance						
Discrimination						
AUC apparent$	0.761 (0.748–0.774)	0.792 (0.780–0.804)	0.773 (0.764–0.782)	0.645 (0.636–0.655)	0.679 (0.669–0.688)	0.653 (0.647–0.660)
AUC validated	0.731 (0.729–0.735)£	0.718 (0.778–0.781) ¶	0.766 (0.764–0.769) £	0.621 (0.617–0.623)£	0.651 (0.648–0.653)¶	0.647 (0.644–0.650) £
Calibration						
Calibration-in-the-large	−0.271£	0.256¶	−0.068£	−0.186£	0.072¶	−0.078£
Calibration slope	0.885£	1.023¶	0.971£	0.926£	1.081¶	0.970£

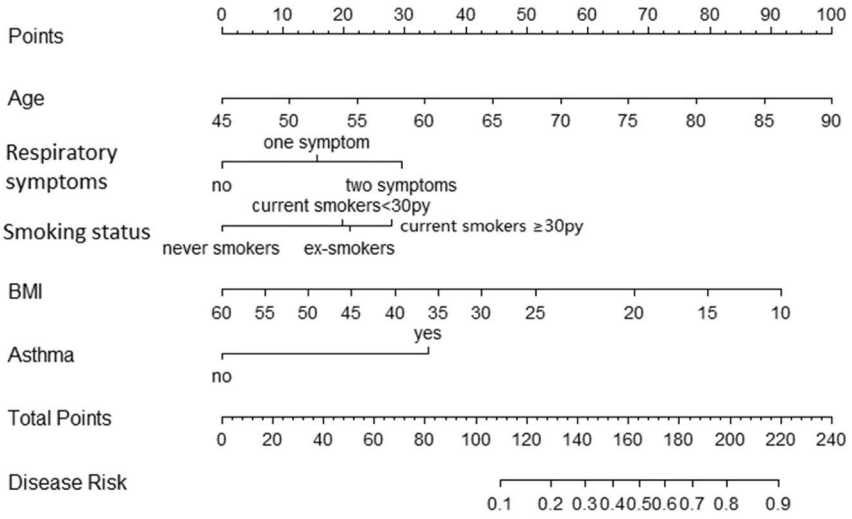
Abbreviations: BMI, body mass index; AUC, area under the receiver operating characteristic.
Airflow obstruction: Forced expiratory volume in 1 s/forced vital capacity ratio < lower limits of normal defined according to equation developed by Ip.
Splines for BMI in model were based on men and women respectively. Knots for BMI in men were at 18.4, 22.4, 24.6, and 28.9 kg/m^2, and that in women were at 18.8, 22.5, 24.9 and 29.5 kg/m^2.
Self-reported respiratory symptoms: cough, phlegm, wheezing for three months per year, and/or dyspnea.
Dyspnea: the British modified Medical Research Council (mMRC) scale ≥2.
$: Performance was evaluated on the data to derive the final model.
£: Estimated by internal validation (bootstrap method).
¶: Estimated by applying the model from the development data set in the validation data set (external validation).
*: P < 0.05.
**: P < 0.01.
***: P < 0.001.



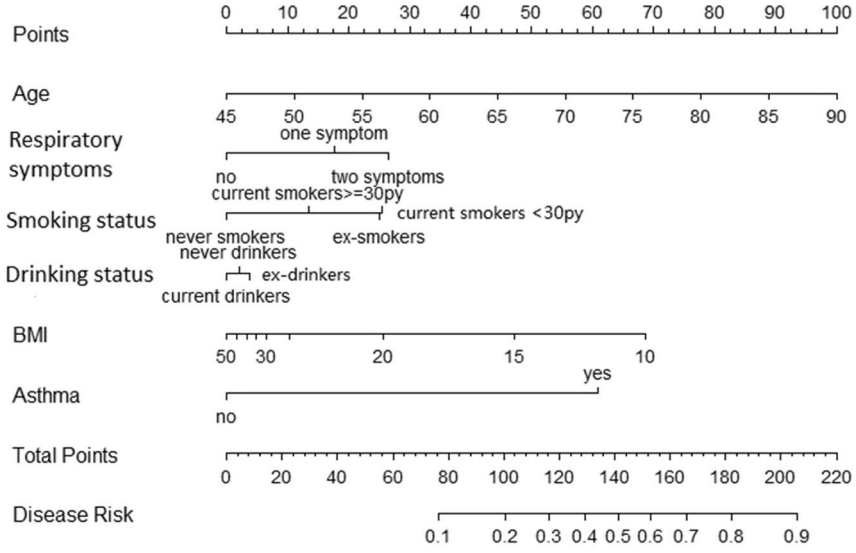
Appendix Fig. 1. Linearity between airflow obstruction and continuous predictors (age and body mass index (BMI)) in development sampleTest for linear trend for age: chi2: 48.3, P < 0.0001
Test for linear trend for BMI: chi2: 39.2, P < 0.0001
Airflow obstruction: Forced expiratory volume in 1 s / forced vital capacity ratio < lower limits of normal.



Appendix Fig. 2. Restricted cubic splines between airflow obstruction and continuous predictors (age and body mass index (BMI)) in development sample (Odds ratio with 95% CI)
Airflow obstruction: Forced expiratory volume in 1 s / forced vital capacity ratio < lower limits of normal.

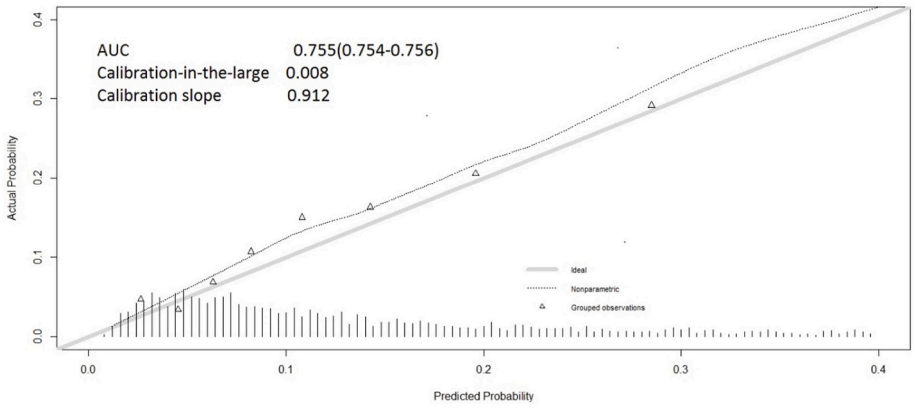


A. Nomogram of the updated prediction model in men

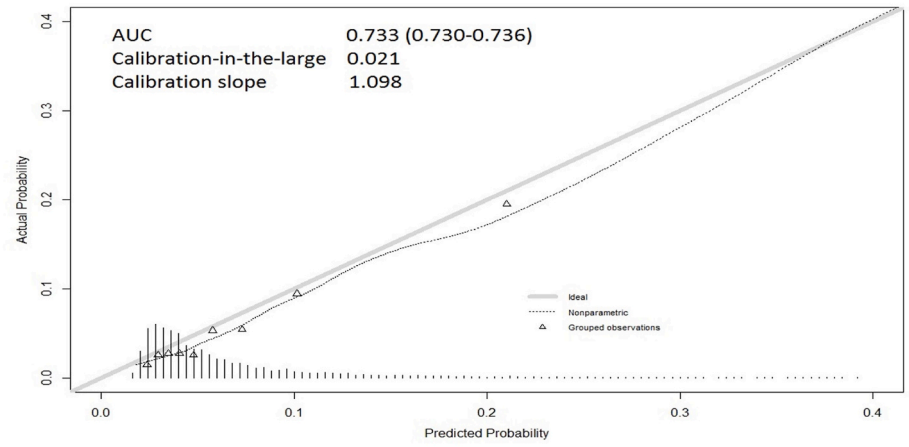


B. Nomogram of the updated prediction model in women

Appendix Fig. 3. Nomogram of the updated prediction model for fixed ratio defined airflow obstruction in men and womenInstructions:
Locate the individual's age on the age axis, draw a line straight upward to the Points axis to get the scores toward the probability of airflow obstruction. Repeat the process for each variable and sum the total score achieved for all predictors. Locate the total score on the Total points axis and draw a line straight down to figure out this individual's probability of having airflow obstruction.
Abbreviation: py: pack years; BMI: body mass index
Self-reported respiratory symptoms: cough, phlegm, wheezing for three months per year, and/or dyspnea
Dyspnea: the British modified Medical Research Council (mMRC) scale $\geq$2
Airflow obstruction: Forced expiratory volume in 1 s
/ forced vital capacity ratio $<$0.70.

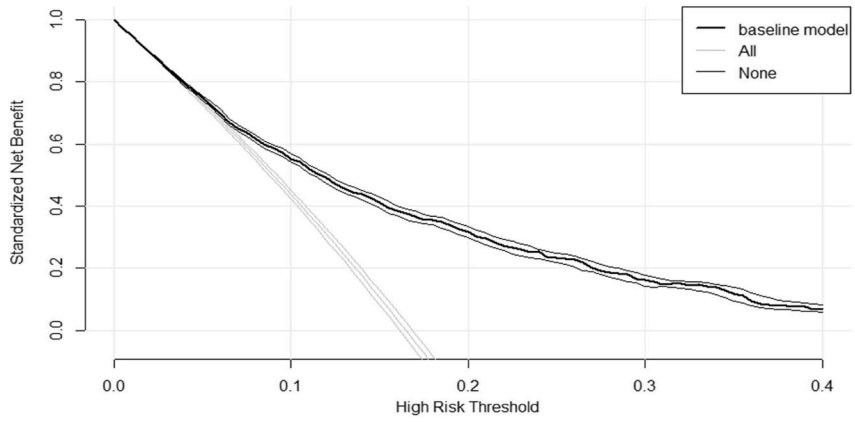


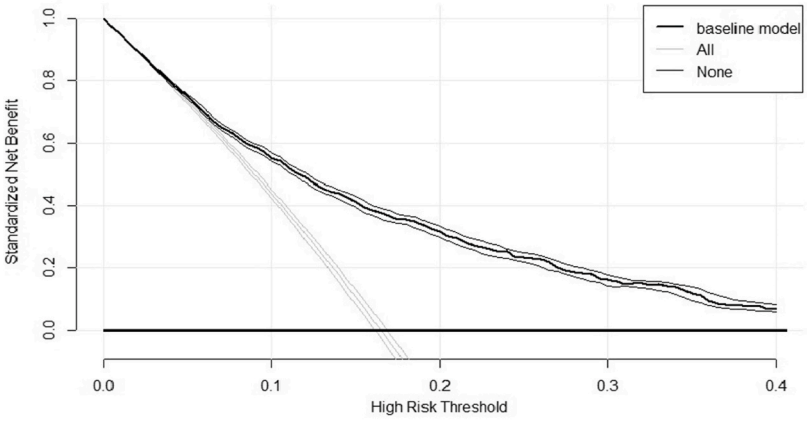
A. Validation plot in men



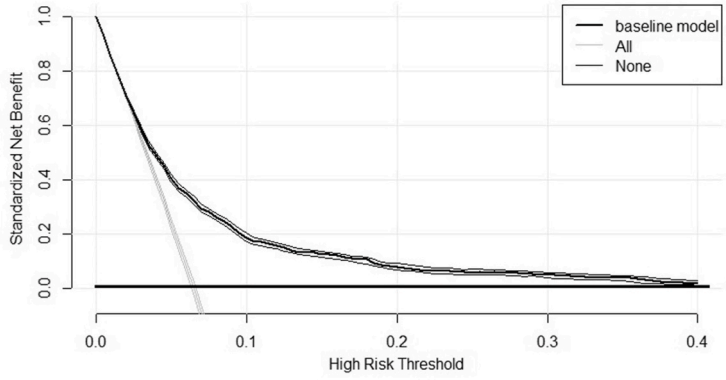
B. Validation plot in women

Appendix Fig. 4. Validation plot for the developed prediction model applied in the sample from GBCS phase 3 (external validation, n = 2096 in men and n = 6299 in women). Calibration-in-the-large calculated as the logistic regression model intercept given that the calibration slope equals 1; Calibration slope in a logistic regression model with the linear predictor as the sole predictor; AUC (area under ROC curve) indicating discriminative ability. Tick marks represent deciles of subjects grouped by similar predicted risk. The distribution of subjects with airflow obstruction is indicated with spikes at the bottom of the graph.
Airflow obstruction: Forced expiratory volume in 1 s
/ forced vital capacity ratio <0.70.





A. Decision curve in men



B. Decision curve in women

Appendix Fig. 5. Decision curves with 95% confidence interval for the final prediction models applied in combined sample. Solid line: Assume no participants are tested, net benefit is zero (no true-positive and no false-positive classifications); Grey line: assume all participants are tested; Black lines: participants are tested if predictions exceed a threshold, with the prediction model. The graph gives the expected net benefit per participants relative to no test in any participants ('None')
Airflow obstruction: Forced expiratory volume in 1 s
/ forced vital capacity ratio <0.70
Standard NB: NB/AO prevalence.

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