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Y.L. and G.Q.Y. were supported in part by grants from the Guangxi Science and Technology Base and Specialized Talent (grants 2017AD23009, 203030301808, and 203050101934). Y.L. and F.H. were supported in part by grants from Guangdong Introducing Innovative and Entrepreneurial Teams (grant 2016ZT06S252) and the General Program of the National Natural Science Foundation of China (grants 81671611 and 81871224). J.W. and S.G.Z. were supported in part by the National Institutes of Health (grant R01 AR059103, National Institutes of Health STAR Award, and grant R61 AR073409).

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

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Available online July 12, 2020.
https://doi.org/10.1016/j.jaci.2020.06.029

A model-based approach for assessing bronchodilator responsiveness in children: The conventional cutoff revisited

To the Editor:

According to international guidelines, asthma diagnosis should be based on identifying both a history of variable respiratory symptoms and a variable expiratory airflow limitation. Therefore, in children with typical respiratory symptoms, the assessment of limitation in expiratory airflow is considered an essential component to support the clinical diagnosis of asthma. In this respect, a greater than or equal to 12% increase in postbronchodilator FEV_1 has been proposed in international guidelines as evidence of airway reversibility.[1] In addition, we have previously shown that children with asthma with larger concentration of serum inflammatory biomarkers experienced a greater number of exacerbations and a greater decline in postbronchodilator FEV_1.[2] However, the validity of the 12% cutoff has been questioned in children.[3] For instance, Dundas et al[4] suggested that a greater than or equal to 9% increase in FEV_1 yields the most acceptable sensitivity (50%) and specificity (86%) to discriminate wheezy children; Tse et al[5] observed that an 8% threshold value is associated with a better performance in differentiating patients with asthma from patients without asthma in a cohort of 1291 children.[5] Therefore, although it is well acknowledged that maximizing sensitivity and specificity is crucial for any diagnostic test, the choice of an optimal bronchodilator response (BDR) cutoff in children is still under debate.

TABLE I. Estimated odds ratio and 95% CIs of the parameters in the segmented logit model: 7.9% and 14.7% in the first rows are the cutoff points identified on the BDR range

Covariates	Odds ratio (95% CI)
Low BDR (BDR ≤ 7.9%)	1.02 (0.99-1.05)
Intermediate BDR (BDR in the range 7.9%-14.7%)	**1.70 (1.36-2.13)**
High BDR (BDR > 14.7%)	0.92 (0.81-1.04)
Demographic characteristics	
Male sex (reference "female")	**1.49 (1.08-2.05)**
Age (y)	0.95 (0.81-1.11)
Height (cm)	1.00 (0.97-1.03)
Weight (kg)	1.02 (1.00-1.04)
Personal factors	
Age of mother at birth (y)	1.00 (0.97-1.03)
Parental history of asthma (reference "no")	**1.56 (1.10-2.21)**
Lower respiratory tract infections within age 3 y (reference "no")	1.29 (0.93-1.80)
Wheeze before age 3 y (reference "no")	**12.31 (8.75-17.32)**
Environmental factors	
Current environmental tobacco exposure (reference "no")	1.34 (0.97-1.86)
Current exposure to traffic in the zone of residence (reference "no")	0.85 (0.56-1.30)
Current mold/dampness exposure (reference "no")	1.21 (0.83-1.77)
Atopy (reference "no")	**4.41 (3.09-6.29)**
Season at time visit (reference "Summer")	
Autumn	0.96 (0.61-1.52)
Winter	**1.78 (1.11-2.85)**
Spring	1.15 (0.73-1.80)

Significant associations are in boldface.

The aim of this study was to assess whether a thorough statistical model taking into account BDR cutoff values and some child characteristics is associated with better performance than the traditional use of BDR cutoff values in supporting the clinical diagnosis through discrimination of outpatient children with steroid-naive asthma from those without asthma. More specifically, we propose to use a regression model with child covariates (eg, age, weight, height, and atopy) as usual linear terms and a piecewise linear relationship on BDR in which cutoff values are properly estimated from the data.

We used data from the CHildhood ASthma and Environment Research (CHASER) study (ClinicalTrials.gov ID: NCT02433275): n = 1146 white children aged 5 to 13 years were enrolled in the study; of them, 660 were diagnosed as those with steroid-naive asthma (324 intermittent, 336 persistent; mean, 8.6. ± 2.32 years) and 486 were without asthma (mean, 8.91 ± 2.32 years). Standardized questionnaires on participants' respiratory symptoms were

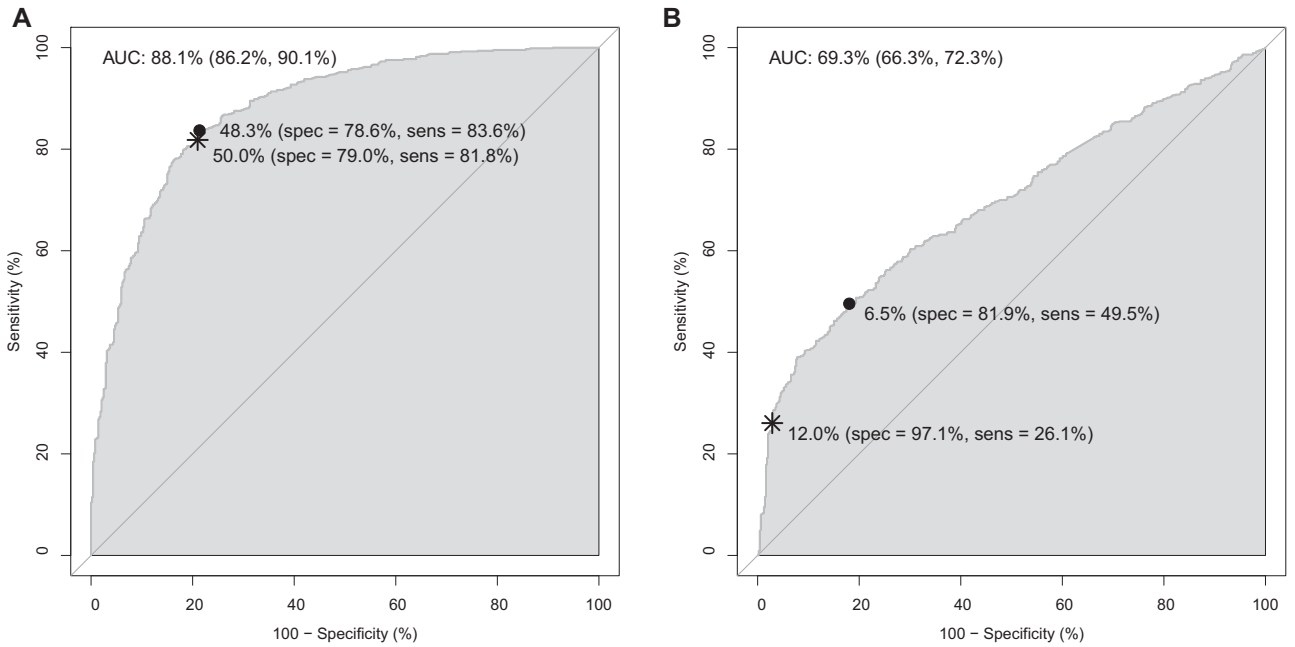

FIG 1. Contrasting 2 ROC curves and corresponding AUC values (95% CI) to spot children with and without asthma. **A,** The fitted probability coming from the segmented logit model is used to discriminate patients with or without asthma; namely, a subject is assessed "asthmatic" when the fitted probability corresponding to his or her covariate pattern is beyond a given probability threshold—the circle and the asterisk refer to 2 possible probability thresholds with associated specificity and sensitivity—the naive 50.0% (midpoint of the probability range), and 48.3% obtained by maximizing the Youden index. **B,** The ROC curve and the corresponding AUC value are obtained when only the BDR values are used to discriminate patients with or without asthma: namely, a subject is predicted "asthmatic" when his or her BDR value is larger than a specified cutoff. The circle and the asterisk refer to 2 possible cutoff values with associated specificity and sensitivity: the conventional 12.0% as suggested in Pellegrino et al[1] and 6.5% obtained by maximizing the Youden index. *sens*, Sensitivity; *spec*, specificity.

completed by parents. Spirometry was performed according to the European Respiratory Society and American Thoracic Society standardization documents[1] using an appropriate device (Cosmed Quark PFT, Rome, Italy).

Spirometry data were transformed into percentages of the predicted values using the Global Lung Initiative reference equations.[6] A greater than or equal to 12% FEV_1 increase 15 minutes after inhalation of 400 μg salbutamol was defined as a positive BDR. Skin prick tests for aeroallergens were performed, and atopy (yes/no) was defined on the basis of a positive puncture skin response after 15 minutes (ie, a wheal ≥3 mm than that achieved with the negative control) at least to 1 of the following allergens: dermatophagoides mix, alternaria, dog and cat dander (indoor), and grass mix, parietaria judaica, cupressus, and olive (outdoor). The clinical diagnosis of asthma (ie, yes/no) was defined as a positive answer to at least 1 of the 3 following questions: "Has the doctor ever told you that your child had asthma?"; "Has your child had wheezing or whistling in the chest in the past 12 months?"; and "Has your child had asthma treatment in the past 12 months?" Among the 660 patients with asthma, 164 answered "yes" to 1 question, 302 to 2 questions, and 194 to all the 3 questions. The 486 children answering no to all the 3 questions were defined as controls. The study was approved by the local Ethics Committee, and informed consent was obtained from parents or legal guardians (N° 8/2014). This article's Online Repository at www.jacionline.org reports further details about materials and methods, including summary statistics about baseline characteristics of the study sample and the spirometry values by group in Tables E1 and E2.

The proposed framework relies on a segmented logit regression model[7] using asthma (yes or no) as the response variable and including demographic, personal and current environmental factors, atopy, and season at the time of the visit as covariates, along with BDR for which threshold values were estimated. To include all subjects in the analyses, missing values for some covariates were imputed as described in this article's Online Repository at www.jacionline.org. Maximum likelihood estimates of model parameter are reported in Table I. In particular, 7.9% and 14.7% are the estimated BDR cutoff values at which the probability of predicting asthma was found to significantly change. The probability of having asthma is almost 0 when the BDR is less than or equal to 7.9%, it significantly rises up when $7.9\% < BDR \leq 14.7\%$, and it gets off in an imperceptible way when the BDR is more than 14.7%. However, such decrease is quite small and it could be due to the low number of children having BDR values above 14.7%, leading to high variability and to a nonsignificant effect. In practice, it means that the probability remains actually unchanged when the BDR is above 14.7%. The entries in the second column represent the odds ratios (point estimates and CIs): a significant risk of predicting asthma was associated with male sex, parental history of asthma, wheeze before age 3 years, atopy, winter *vs* summer at the time of the visit, and a BDR increase in the range 7.9% to 14.7%.

Using child information and the parameter estimates of the fitted segmented regression (covering also the nonsignificant coefficients), the probability of having asthma can be computed, as detailed in this article's Online Repository at www.jacionline.org. For example, an 8-year-old girl, weighing 35 kg and 132 cm tall, with 32-year-old mother at birth, parental history of asthma, lower respiratory tract infections within age 3 years, current environmental tobacco exposure, current exposure to traffic in the zone of residence, current mold/dampness exposure, atopy, no wheezing before age 3 years, visited in summer, and with a BDR of 3%, exhibits a 32% probability of having asthma. Furthermore, a similar girl without any risk factor and a 15% BDR has a 65.1% probability of having asthma. We propose to exploit such model-based probability to support the clinical diagnosis, namely, to assess as asthmatic the patient having his or her predicted probability larger than a given threshold. At any fixed probability threshold, sensitivity and 100 − specificity may be obtained by comparing the *true* child asthmatic status with respect to the *predicted* child asthmatic status. As the threshold changes, sensitivity and 100 − specificity values are obtained and the resulting receiver-operating characteristic (ROC) curve is displayed in Fig 1, *A*, along with the area under the curve (AUC) value. Also, the points corresponding to 2 possible thresholds on the probability range are displayed: the naive 50.0% and 48.3%. The former is the simple midpoint of the probability range, whereas the latter is obtained by maximizing both sensitivity and specificity, namely, the so-called Youden criterion, which is usually used to summarize the performance of a dichotomous diagnostic test.[8] As an alternative to the proposed model-based approach, Fig 1, *B*, displays the ROC curve based on BDR values only, namely, predicting the asthmatic status if the BDR value is larger than a specified cutoff. Then, the ROC curve along with its AUC value and CI are obtained by considering different cutoff values on the BDR scale. Two points referring to the conventional cutoff proposed in Pellegrino et al[1] (12.0%) and the one determined by the Youden criterion (6.5%) are also reported.

The use of the fitted probabilities derived from the logit regression model yields quite satisfactory performance, with somewhat high values of AUC (almost 90%) and sensitivity and specificity (90.1% and 86.2%, respectively): there is no substantial difference when 50.0% or 48.3% is used as probability threshold to predict the asthmatic status. However, the test based on BDR can discriminate children with asthma from those without asthma with only moderate accuracy (AUC just below 70%): the conventional value 12% yields a very high specificity (97.1%) but a poor sensitivity (26.1%), whereas the 6.5% cutoff obtained via the Youden statistic achieves a specificity of 81.9% and a sensitivity of 49.5%. Quite similar AUC values were obtained when stratifying the analysis by sex: 68.2% (95% CI, 64.3%-72.1%) for males and 70.7% (95% CI, 65.9%-75.5%) for females.

In addition to ROC curves, the classification rules based on the fitted probability from segmented logit regression and those relying on BDR only were compared in terms of predictive capability, too. Results, obtained via 10-fold cross-validation, again emphasize the outperformance of the proposed model-based approach (correct classification rate about 81% using the 2 probability thresholds, 50% and 48.3%) with respect to the traditional ones based on BDR-value only (correct classification rates 56.1% and 61.0%, using the cutoffs 12.0% or 6.5%, respectively). Robustness of our results was assessed by fitting the same segmented logit model but (1) without 5-year-old children; (2) using another definition of BDR[9] (see Tables E3 and E4 in this article's Online Repository at www.jacionline.org); and (3) estimating just a single breakpoint on the BDR range. Further discussion is included in this article's Online Repository at www.jacionline.org. As expected, findings are substantially unchanged, making our estimates somewhat robust to different measurements of bronchodilator responsiveness and also to different number of breakpoints.

The good performance of the proposed model-based approach highlights that keeping into account several subject characteristics might help clinicians to improve accuracy in asthma diagnosis. However, despite such good performance, it should be acknowledged that no cutoff might provide a thorough and standalone diagnostic accuracy, because asthma remains a clinical diagnosis. In fact, even if high BDR can be strongly suggestive of asthma, a low BDR does not exclude the diagnosis. Indeed, a bronchodilator response may not be present on a given occasion if, for example, lung function is near normal or if obstruction is due to airways remodeling.

For instance, in our study sample 14 children without asthma diagnosis had BDR values larger than 12%, and 8 children had BDR more than 14.7%. Specifically, 8 of the 14 children had current symptoms of rhinitis, whereas the others had atopic diseases such as eczema, urticaria, and food allergy.

For clinicians interested in assessing it, we mention that the proposed model-based approach and consequent classification is usable via a dynamic nomogram, freely accessible at https://gianlucasottile.shinyapps.io/DynNomapp/, which returns the predicted probability with the 95% CI when all covariate values, as those listed in Table I, are filled in the form. As discussed in this article's Online Repository at www.jacionline.org, if some information is missing or not available, it is possible to enter "unknown" in the form to exclude the term: a new model is fitted and the probability estimate and CI are returned. If the predicted probability is high (>50%) and it matches the clinical diagnosis, the child has an increased likelihood of having asthma. To quantify performance when a covariate is ruled out, Table E5 in this article's Online Repository at www.jacionline.org reports the average correct classification errors in the training and test sets obtained by applying the 10-fold cross-validation excluding one of the categorical variables each time (in case of missing information).

Finally, it should be acknowledged that the proposed framework has been built up on white children living in Italy. Further studies are warranted to validate the nomogram before a possible clinical use in childhood asthma practice also in other populations.

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Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

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Available online August 7, 2020.
https://doi.org/10.1016/j.jaci.2020.07.029

Identification of whole blood gene expressions correlated with responsiveness to benralizumab

To the Editor:

Severe eosinophilic asthma is a heterogeneous condition.[1] Benralizumab is an mAb that binds to the alpha chain of the IL-5 receptor and is used to treat this condition worldwide.[2-4] However, not all patients with eosinophilic asthma will benefit from benralizumab due to the heterogeneity of this condition. Forty-one patients with severe eosinophilic asthma in this study showed variable clinical responses to benralizumab, although peripheral blood eosinophils disappeared completely in all patients 4 months after the start of treatment. In the current study, the goal was to identify variable gene expression patterns in response to benralizumab and to determine whether any specific gene expression patterns were correlated with clinical responsiveness to benralizumab. All participating patients with severe asthma required treatment with high-dose inhaled corticosteroids plus long-acting beta agonists. Some of them required maintenance systemic corticosteroids. All patients had blood eosinophil counts of at least 150 cells/μL in their blood examinations over the last 2 years before the initiation of benralizumab. To examine molecular heterogeneity underlying the variable clinical responses, using a comprehensive gene expression analysis of whole blood cells, the effects of 4 months of treatment with benralizumab on gene expressions of whole blood cells were initially characterized, and changes in inflammatory markers and immune-related signaling pathways were identified. The study populations and methods are described in detail in this article's Online Repository at www.jacionline.org.

There were 161 differentially expressed (DE) genes in the whole blood cells of 41 patients between baseline (0M) and 4 months after benralizumab treatment (4M) with significant differences (false discovery rate [FDR]-adjusted $P < .05$) and with more than 2-fold changes. Four months after benralizumab treatment, significant reductions in the expressions of genes associated with eosinophilic inflammatory responses, such as *SIGLEC8*, *ALOX15*, *PRSS33*, *CCL23*, and *IL5RA*, were observed (see Tables E1 and E2 in this article's Online Repository at www.jacionline.org). These results reflect the effect of benralizumab to induce direct, rapid, and nearly complete depletion of eosinophils through an apoptotic process involving natural killer cells.[5]

The heatmap clearly shows the separation of baseline and postbenralizumab samples according to these 161 genes (Fig E1). Three large clusters were identified: 2 clusters, A and B, consisted of gene expression data in the baseline samples, and the other cluster, C, consisted of gene expression data in the samples of 4 months after treatment. Cluster A was recognized as a high-altered cluster with benralizumab treatment because changes in gene expressions due to treatment were greater. Cluster B was recognized as a low-altered cluster with benralizumab treatment because changes in gene expressions due to treatment were modest. We hypothesized that DE genes between these 2 clusters at baseline (high-altered and low-altered clusters) could have an impact on the variable clinical responsiveness to benralizumab. Sixty-two DE genes were subsequently identified by the comparison between these 2 clusters (FDR-adjusted $P < .01$ and with more than 3-fold changes); 29 and 33 mRNAs were significantly upregulated and downregulated, respectively, in the whole blood cells of cluster B compared with those of cluster A (Fig 1; see Table E3 in this article's Online Repository at www.jacionline.org). Upregulated genes were significantly enriched in gene ontology (GO) categories related to neutrophils, such as serine hydrolase activity, neutrophil degranulation, and neutrophil activation (see Table E4 in this article's Online Repository at www.jacionline.org). Downregulated genes were significantly enriched in GO categories associated with type 2 inflammation and eosinophils, such as IL-33 receptor activity and IL-5 receptor activity (Table E4).

Hierarchical clustering of the baseline samples using only these 62 genes eventually identified 4 whole blood transcriptional endotypes of severe asthma (TESA) (Fig 1). All patients in TESA cluster 2 belonged to the high-altered cluster (cluster A). Three other TESA clusters belonged to the low-altered cluster (cluster B). To determine whether these 4 defined TESA clusters corresponded to distinct phenotypes of severe asthma, the physiologic and clinical responses to benralizumab were compared among these clusters (Table I).

TESA cluster 1, in which 83% of the patients were regularly taking oral corticosteroid (OCS), was characterized by lower numbers of peripheral eosinophils, higher numbers of peripheral neutrophils, and higher expressions of genes related to neutrophil activities (Table I and Fig 1). In addition, none of the patients in TESA cluster 1 were super responders to benralizumab treatment. Given that all patients on OCS treatment in the study had elevated blood eosinophil counts (>300 cells/μL) before initiation of OCS treatment, patients with poor responsiveness both to OCS and to benralizumab in TESA 1 might possibly have a mixed type of inflammation consisting of eosinophilic and noneosinophilic inflammation. The finding that nonresponsiveness to benralizumab is characterized by the neutrophil-related gene expressions in the current study supports the contention that the coexistence of noneosinophilic inflammation in patients with severe eosinophilic asthma could contribute to poor responsiveness to benralizumab, as well as to OCS. In TESA cluster 2, the largest cluster (n = 19), 53% of

METHODS

Study design and study population

Between September 2011 and January 2019, 1146 children, part of the CHildhood ASthma and Environment Research Study, aged 5-13 years, were recruited at the outpatient clinic of Paediatric Allergology & Pulmonology of IBIM CNR of Palermo, Italy.

Data collection

The parents or legal guardians were interviewed through a modified version of the SIDRIA questionnaire,[E1] including questions regarding demographic characteristics, parental history of asthma, and current outdoor and indoor environmental exposures. The diagnosis of asthma was defined as a positive answer to at least 1 of the 3 following questions: "Has the doctor ever told you that your child had asthma?"; "Has your child had wheezing or whistling in the chest in the past 12 months?"; and "Has your child had asthma treatment in the past 12 months?" Among the 660 patients with asthma, 164 answered "yes" to 1 question, 302 to 2 questions, and 194 to all the 3 questions. The 486 children answering "no" to all the 3 questions were defined as controls. Current rhinitis was defined as a positive response to the question: "In the past 12 months, has your child ever had a problem with sneezing, or a runny nose, or a blocked nose when he/she did not have a cold or flu?" Coexistent atopic diseases were also investigated. Patients with history of any other chronic pulmonary or systemic disease were excluded from the study. Subjects who were on regular inhaled corticosteroid treatment were also excluded. Spirometry, bronchodilator reversibility, and atopy were assessed.

Spirometry was performed through a portable flow turbine spirometer (Pony FX portable spirometer, Cosmed), according to American Thoracic Society/European Respiratory Society guidelines.[E2] Spirometry measurements were expressed as percentage of the predicted values and z scores (see Table E2), using the Global Lung Initiative reference values.[E3] BDR was defined as the percentage change in FEV_1 measured 15 minutes after inhalation of 400 μg salbutamol administered via a metered dose inhaler through a plastic spacer device (Aerochamber), namely:

$$\frac{(\text{post FEV}_1 - \text{baseline FEV}_1)}{\text{baseline FEV}_1} \times 100$$

As reported in the main article, for sensitivity analysis we also considered an alternative measurement of BDR based on Dales et al,[E4] which is relatively stable across sex-age-height groups, namely:

$$\frac{(\text{post FEV}_1 - \text{baseline FEV}_1)}{\text{predicted normal FEV}_1} \times 100$$

As expected, the 2 measurements were strongly correlated (see Fig E1). It is worth noting the large portion of subjects having sizable negative measurements, likely because many of these children were younger than 7 years and had on average "D quality" curve (Table 10 of the ATS-ERS spirometry standardization update[E5]).

Statistical analyses

Analyses were performed using R (3.6.0) statistical analysis software. Distributions of missing data among the observed covariates are reported in Fig E2. To use all available data and to maximize information, we first imputed all missing data using the *MICE*[E6] package in R. This approach performs multiple imputations for incomplete multivariate data by chained equations and Gibbs sampling algorithm, yielding "plausible" synthetic values given other columns in the data. The segmented logit regression models, the ROC curves, and the nomogram were obtained using the R packages segmented,[E7] *pROC*,[E8] and *DynNom*,[E9] respectively.

For all statistical analyses, a P value of less than .05 was considered statistically significant.

The segmented model

Segmented or broken-line models are regression models wherein the relationships between the response and 1 or more explanatory variables are piecewise linear, namely, represented by 2 or more straight lines connected at unknown values, usually referred as breakpoints. A segmented relationship between the mean response $\pi = E[Y]$ and the variable Z is modeled by adding in the linear predictor the following terms $\beta_1 Z + \beta_2 (Z - \psi)_+$, where $(Z - \psi)_+ = (Z - \psi) \times I(Z > \psi)$ and $I(\cdot)$ is the indicator function that assumes the value 1 when the statement is true, and 0 otherwise. According to such parameterization, β_1 is the left slope, $\beta_1 + \beta_2$ is the right slope, and ψ is the breakpoint. The segmented logit model in the article reads as

$$\begin{aligned}\text{logit}(\pi) = {} & \beta_0 + \beta_1 \text{BDR} + \beta_2 (\text{BDR} - \psi_1)_+ + \beta_3 (\text{BDR} - \psi_2)_+ \\ & + \beta_4 X_1 + \beta_5 X_2 + \beta_6 X_3 + \beta_7 X_4 + \beta_8 X_5 + \beta_9 X_6 + \beta_{10} X_7 + \beta_{11} X_8 \\ & + \beta_{12} X_9 + \beta_{13} X_{10} + \beta_{14} X_{11} + \beta_{15} X_{12} + \beta_{16} X_{13}\end{aligned}$$

where $\pi = E[Y]$ is the probability of being asthmatic conditional to covariates, Y is the response variable assumed to follow a binomial distribution, and X_j, $j = 1, \ldots, 13$, are the risk factors included in the model (following the order reported in Table I). Parameter estimates, regression coefficients beta and breakpoints ψ, were obtained by maximizing the binomial log likelihood. The number of breakpoints accounting for the BDR effect was selected by the Bayesian information criterion: 2 breakpoints provided the best Bayesian information criterion value, and although a different number of breakpoints could be estimated, the relevant performance would be deteriorated, leading, for instance, to a lower AUC value.

The estimated BDR effect with 2 breakpoints is displayed in Figure E3: the probability of being asthmatic is negligible and does not change if the BDR is less than 7.9%, it increases as the values of the BDR increase in the range 7.9% to 14.7%, and it slightly decreases when the BDR is more than 14.7%. The drop after the second breakpoint could appear somewhat weird; however, uncertainty is quite large and the associated odds ratio is not significant (see Table I in the main text), suggesting that the coefficient could be actually assumed to be 0. In other words, the probability of being asthmatic does not change when the BDR is more than 14.7%.

Given the maximum likelihood parameter estimates, the predicted probability is computed via

$$\hat{\pi} = \frac{\exp(\widehat{\beta_0} + \widehat{\beta_1} X_1 + \cdots + \widehat{\beta_{13}} X_{13}.)}{1 + \exp(\widehat{\beta_0} + \widehat{\beta_1} X_1 + \cdots + \widehat{\beta_{13}} X_{13})}$$

The validation step

As reported in the main text, the predictive capability of the model was assessed via 10-fold cross-validation. Ten-fold cross-validation consists into partitioning the whole data set into 10 folds, leaving out 1 partition at time in turn to be used as the test sample; therefore, each time we used 9 of 10 partitions to train the model and the remaining 1 of 10 partition to test it, for computing the correct classification rate. In each fold, patients with and without asthma were selected proportionally to their dimension in the study sample. The correct classification rate or accuracy is defined as (TP + TN)/(TP + TN + FP + FN), where TP = True positive or true asthmatic patients, TN = True negative or true nonasthmatic patients, FP = False positive, and FN = False negative.

The dynamic nomogram

The dynamic nomogram was built using the fitted segmented logit model containing all the terms in Table I. Our nomogram may help clinicians to improve the accuracy of diagnosis of asthma by considering patient information that may be easily collected. More specifically, values for covariates listed in Table I have to be supplied to get the predicted probability. However, if some information is missing or not available, it is possible to insert "unknown" to exclude the term: a new segmented model is fitted without that variable and the output is used to predict the probability of being asthmatic. To quantify performance when a covariate is ruled out, Table E5 reports the average correct classification errors in the training and test sets obtained by

applying the 10-fold cross-validation excluding one of the categorical variables each time (in case of missing information): results highlight that almost in all cases the model works reasonably well in predicting the probability of being asthmatic, with the exception of "Wheeze before 3 years of age" which, however, is unlikely unknown by any physician taking the medical history of a child with asthma. Furthermore, information on the quantitative variables, child and mother age, height, and weight is supposed to be always known to the medical doctor and therefore corresponding values have to be filled in the nomogram.

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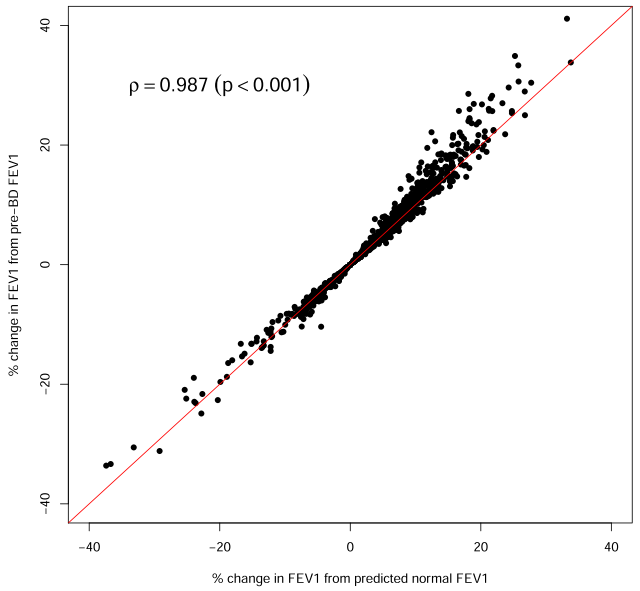

FIG E1. Scatterplot of the 2 measurements of BDR: % change in FEV_1 from pre-BD FEV_1 vs % change in FEV_1 from predicted normal FEV_1. *BD*, Broncodilator.

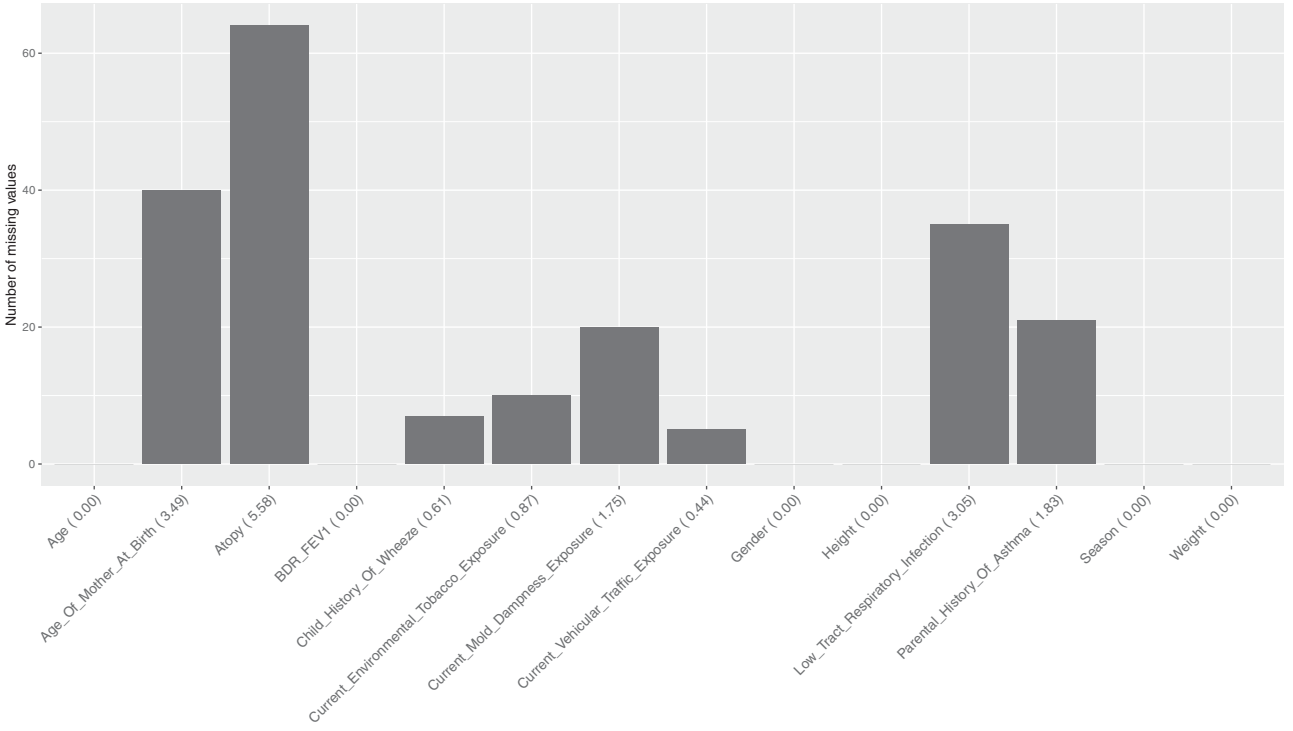

FIG E2. Counts of missing values for each variable in the study. Numbers after the variable names refer to percentages.

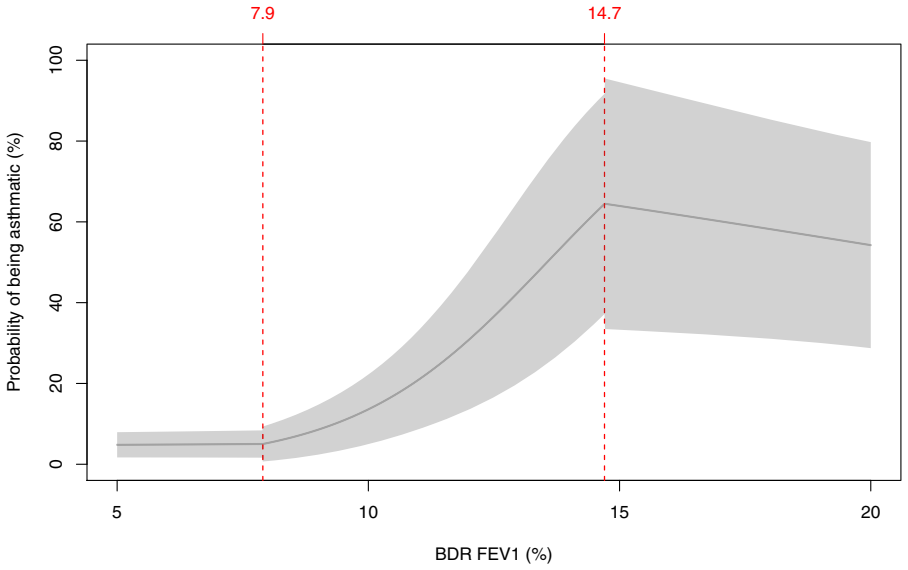

FIG E3. Probability of being asthmatic predicted from the segmented logit model when the values of BDR vary between 5 and 20 and all the remaining variables, categorical and continuous, are held fixed at their baseline levels and at the mean values, respectively.

TABLE E1. Characteristics of the study sample

Characteristic	All	Patients without asthma	Patients with asthma	*P* value
Children	1146	486 (42.4)	660 (57.6)	
Age (y)	8.78 ± 2.32	8.91 ± 2.32	8.69 ± 2.32	.112
Female sex	450 (39.27)	221 (45.47)	229 (34.70)	**<.001**
Height (cm)	132.73 ± 14.43	133.02 ± 14.40	132.52 ± 14.47	.563
Z score	0.22 ± 1.12	0.15 ± 1.13	0.27 ± 1.11	.082
Weight (kg)	34.76 ± 13.07	34.47 ± 12.77	34.97 ± 13.30	.520
BMI (kg/m^2)	19.11 ± 4.14	18.93 ± 4.11	19.25 ± 4.16	.206
Z score	1.06 ± 1.51	0.93 ± 1.54	1.16 ± 1.49	**.014**
Personal factors				
Age of mother at birth (y)	31.87 ± 4.99	32.40 ± 4.91	31.47 ± 5.02	**.019**
Parental history of asthma	347 (30.84)	115 (24.01)	232 (35.91)	**<.001**
Lower respiratory tract infections within age 3 y	385 (45.03)	119 (32.69)	266 (54.18)	**<.001**
Wheeze before age 3 y	619 (54.35)	118 (24.48)	501 (76.26)	**<.001**
Current rhinitis	599 (56.19)	237 (53.50)	362 (58.11)	.152
Environmental factors				
Current environmental tobacco smoke exposure	459 (40.40)	171 (35.33)	288 (44.17)	**.003**
Current exposure to traffic in the zone of residence	937 (82.12)	411 (85.09)	526 (79.94)	**.030**
Current mold/dampness exposure	260 (23.09)	97 (20.08)	163 (25.35)	**.045**
Atopy	739 (68.30)	247 (54.53)	492 (78.22)	**<.001**
Season at the time of the visit				.057
Winter	268 (23.39)	100 (20.58)	168 (25.45)	
Spring	317 (27.66)	143 (29.42)	174 (26.36)	
Summer	254 (22.16)	121 (24.90)	133 (20.15)	
Autumn	307 (26.79)	122 (25.10)	185 (28.03)	
GINA control				
Well controlled			248 (37.57)	
Partially controlled			160 (24.24)	
Not controlled			252 (38.18)	
No. of exacerbation in last 12 mo			3.41 (3.56)	

GINA, Global Initiative for Asthma.

Data are presented as mean ± SD or n (%); *P* values come from a *t* test or a χ^2 test. Significant associations are in boldface.

TABLE E2. Spirometry parameters by group

Parameter	Patients without asthma (n = 486)	Patients with asthma (n = 660)	*P* value
FEV_1			
Absolute	1.80 ± 0.53	1.68 ± 0.52	**<.001**
% predicted	100.32 ± 11.76	94.26 ± 12.37	**<.001**
Z score	0.03 ± 0.98	−0.48 ± 1.04	**<.001**
BDR FEV_1 (%)	1.35 ± 7.02	6.79 ± 8.81	**<.001**
FVC			
Absolute	2.03 ± 0.64	1.97 ± 0.65	0.079
% predicted	99.65 ± 12.67	96.67 ± 12.77	**<.001**
Z score	−0.04 ± 1.04	−0.28 ± 1.06	**<.001**
FEV_1/FVC			
Absolute	0.89 ± 0.06	0.86 ± 0.08	**<.001**
% predicted	100.36 ± 6.61	97.21 ± 8.17	**<.001**
Z score	0.14 ± 0.98	−0.29 ± 1.15	**<.001**
FEF_{25-75}			
Absolute	2.13 ± 0.68	1.87 ± 0.68	**<.001**
% predicted	95.55 ± 19.60	85.39 ± 22.79	**<.001**
Z score	−0.23 ± 0.87	−0.69 ± 1.03	**<.001**

FEF_{25-75}, Forced expiratory flow at 25%-75% of the FVC; *FVC*, forced vital capacity. Data are presented as mean ± SD; *P* values come from a *t* test or a χ^2 test. Significant associations are in boldface.

TABLE E3. Estimated odds ratio and 95% CIs of the parameters in the segmented logit model excluded children aged 5 y

Covariates	Odds ratio (95% CI)
Low (BDR < 7.9%)	1.01 (0.98-1.04)
Intermediate (BDR in the range 7.9%-14.7%)	**1.96 (1.42-2.72)**
High (BDR > 14.7%)	0.91 (0.81-1.03)
Demographic characteristics	
Male sex (reference "female")	**1.48 (1.05-2.09)**
Age (y)	0.92 (0.79-1.09)
Height (cm)	1.00 (0.97-1.03)
Weight (kg)	1.02 (1.00-1.05)
Personal factors	
Age of mother at birth	1.00 (0.96-1.03)
Parental history of asthma (reference "no")	**1.57 (1.09-2.27)**
Lower tract respiratory infections (reference "no")	1.18 (0.83-1.67)
Wheeze before age 3 y (reference "no")	**13.22 (9.23-18.95)**
Environmental factors	
Current environmental tobacco exposure (reference "no")	1.35 (0.95-1.90)
Current exposure to traffic in the zone of residence (reference "no")	0.94 (0.60-1.47)
Current mold/dampness exposure (reference "no")	1.21 (0.81-1.82)
Atopy (reference "no")	**5.10 (3.48-7.48)**
Season at time of visit (reference "Summer")	
Autumn	0.89 (0.55-1.45)
Winter	**1.91 (1.16-3.13)**
Spring	1.13 (0.70-1.81)

Significant associations are in boldface.

TABLE E4. Estimated odds ratio and 95% CIs of the parameters in the segmented logit model using BDR-PD definition

Covariates	Odds ratio (95% CI)
Low (BDR < 6.5%)	1.01 (0.98-1.05)
Intermediate (BDR in the range 6.5%-14.3%)	**1.56 (1.31-1.86)**
High (BDR > 14.3%)	0.89 (0.75-1.06)
Demographic characteristics	
Male sex (reference "female")	**1.45 (1.05-2.00)**
Age (y)	0.96 (0.83-1.12)
Height (cm)	1.00 (0.97-1.03)
Weight (kg)	1.02 (0.99-1.04)
Personal factors	
Age of mother at birth	0.97 (0.94-1.00)
Parental history of asthma (reference "no")	**1.49 (1.05-2.11)**
Lower tract respiratory infections (reference "no")	**1.69 (1.22-2.34)**
Wheeze before age 3 y (reference "no")	**11.92 (8.49-16.73)**
Environmental factors	
Current environmental tobacco exposure (reference "no")	1.28 (0.92-1.77)
Current exposure to traffic in the zone of residence (reference "no")	0.83 (0.55-1.27)
Current mold/dampness exposure (reference "no")	1.17 (0.80-1.71)
Atopy (reference "no")	**3.97 (2.79-5.65)**
Season at time of visit (reference "Summer")	
Autumn	0.98 (0.62-1.53)
Winter	**1.78 (1.11-2.86)**
Spring	1.20 (0.77-1.88)

PD, PreDicted.
Significant associations are in boldface.

TABLE E5. Average correct classification errors rate in the training and test sets obtained by applying the 10-fold cross- validation to the segmented model excluding one of the categorical variables each time

	Correct classification error	
Excluded variable	**Train set**	**Test set**
Parental history of asthma	81.0	80.4
Lower tract respiratory infections	81.1	80.5
Wheeze before age 3 y	72.2	70.2
Current environmental tobacco exposure	81.1	80.1
Current exposure to traffic in the zone of residence	81.0	80.3
Current mold/dampness exposure	80.8	80.7
Atopy	80.0	79.8
Season at time of visit	80.9	80.4