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Identifying patients at risk for severe exacerbations of asthma: development and external validation of a multivariable prediction model

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ABSTRACT

Background Preventing exacerbations of asthma is a major goal in current guidelines. We aimed to develop a prediction model enabling practitioners to identify patients at risk of severe exacerbations who could potentially benefit from a change in management.

Methods We used data from a 12-month primary care pragmatic trial; candidate predictors were identified from GINA 2014 and selected with a multivariable bootstrapping procedure. Three models were constructed, based on: (1) history, (2) history+spirometry and (3) history+spirometry+FeNO. Final models were corrected for overoptimism by shrinking the regression coefficients; predictive performance was assessed by the area under the receiver operating characteristic curve (AUROC) and Hosmer–Lemeshow test. Models were externally validated in a data set including patients with severe asthma (Unbiased BIOmarkers in PREDiction of respiratory disease outcomes).

Results 80/611 (13.1%) participants experienced ≥1 severe exacerbation. Five predictors (Asthma Control Questionnaire score, current smoking, chronic sinusitis, previous hospital admission for asthma and ≥1 severe exacerbation in the previous year) were retained in the history model (AUROC 0.77 (95% CI 0.75 to 0.80); Hosmer–Lemeshow p value 0.35). Adding spirometry and FeNO subsequently improved discrimination slightly (AUROC 0.79 (95% CI 0.77 to 0.81) and 0.80 (95% CI 0.78 to 0.81), respectively). External validation yielded AUROCs of 0.72 (95% CI 0.70 to 0.73; 71 to 0.74 and 0.71 to 0.73) for the three models, respectively; calibration was best for the spirometry model.

Conclusions A simple history-based model extended with spirometry identifies patients who are prone to asthma exacerbations. The additional value of FeNO is modest. These models merit an implementation study in clinical practice to assess their utility.

INTRODUCTION

Asthma is a common, chronic inflammatory disease of the airways, which is characterised by airflow limitation and the fluctuating course of its symptoms: wheezing, dyspnoea and cough.[1] These symptoms are influenced by a wide variety of triggers, such as viral airway infections, exposure to inhaled allergens, cigarette smoke and/or exercise.[1] Occasionally, patients experience sudden flare-ups of symptoms requiring prompt change in treatment (exacerbations),[2] which result in absenteeism from work or school and additional healthcare utilisation.
[3] Besides controlling symptoms, reducing the risk of exacerbations is a major treatment goal in current asthma guidelines. Some known risk factors for exacerbations, such as current smoking, are modifiable, and stepping up asthma treatment can reduce the risk of exacerbations.[4] Therefore, identifying patients at high risk for exacerbations is useful;[5] in particular, it could guide practitioners to administer appropriate interventions at an early stage to those patients who are likely to benefit.

Moreover, according to global initiative for asthma (GINA),[1] assessment of asthma control should include assessment both of current symptom control and of future risks for adverse outcomes.

Several markers appear to be associated with future asthma exacerbations, for example a history of previous exacerbations[6] and low FEV1.[7] Composite scores largely based on symptoms such as Asthma Control Questionnaire (ACQ)[8] and the Asthma Quality of Life Questionnaire predict exacerbations better than single variables.[9]

Currently however, multivariable prediction models for exacerbations in primary care asthma population are scarce. Although representing a step in the right direction, some existing models suffer from one or more drawbacks that limit their broad application, such as lacking proper assessment of predictive properties[10] and development in populations with high medication use and/or exacerbation history.[11]–[13] Hence, there is a need for a prediction model to identify patients at risk for exacerbations of asthma, which could be more relevant to clinical practice. The aim of the present study was to construct and validate a prediction model for

exacerbations of asthma in adults in a heterogeneous asthma population. For this purpose, we analysed data from a pragmatic trial in primary care, in which exacerbations during 12 months of follow-up were recorded and validated the models in an external data set.

METHODS

Cohort description

The model derivation cohort consisted of 611 participants who participated in a pragmatic trial with 12-month follow-up assessing patient preferences and cost-effectiveness of three treatment strategies targeted at achieving different levels of asthma control. Details of the methods and results of the Asthma Control Cost-Utility RAndomized Trial Evaluation (ACCURATE) trial are reported elsewhere.[14] Eligible patients, recruited from general practices in three regions of the Netherlands, were adults with a doctor's diagnosis of asthma who were prescribed inhaled corticosteroids in any dose or form at least once during the previous year. Exclusion criteria were oral corticosteroid therapy within 1 month before enrolment, significant co-morbidity (at the discretion of the practitioners) and insufficient mastery of the Dutch language. At baseline, online questionnaires on patient asthma characteristics, including the ACQ,[8] were completed, spirometry was performed, a venous blood sample was collected to determine total IgE and specific IgE against house dust mite, cat, grass and birch pollens and FeNO was measured (details in online supplementary appendix I). During the study, maintenance asthma medications were adjusted at 3-month intervals, based on 5-item ACQ and spirometry with or without FeNO.[14] As no significant differences were observed in exacerbations between the three treatment strategies,[14] we combined the data for the present analysis.

Candidate predictors

Candidate predictors were identified from the GINA 2014 report,[1] which lists 17 independent risk factors for exacerbations.
We were able to operationalise 14 of these variables from the ACCURATE baseline data set (table 1). We were unable to assess inhaler technique, sputum eosinophilia or blood eosinophilia or pregnancy. Additionally, we evaluated the value of adding FeNO to the model; resulting in 15 predictors assessed.

Outcome

The dependent variable was: one or more severe exacerbations, based on the American Thoracic Society/European Respiratory Society (ATS/ERS) recommendation[15]: as a course of oral corticosteroids for at least 3 days, and/or an emergency department visit or a hospitalisation due to increased symptoms of asthma.

[TABLE 1]

Statistical analysis

Handling of missing data

Eighty-four per cent of the patients had complete data for the candidate predictors; missing values were due to unfinished online questionnaires. In 7% of patients, information on one variable was missing and 1% of patients lacked information on ≥

5 variables from the 15 candidate predictors. Data on severe exacerbations were nearly complete as prescriptions for systemic corticosteroids were obtained from patients' pharmacies after the study; recall bias for emergency department visits or hospitalisations from the three monthly questionnaires was deemed low. We multiply imputed missing values (generating 10 data sets) by iterative chained equations using all variables to replace missing values.[16]

Development of the model

Fourteen candidate predictors identified from GINA (table 1) plus FeNO were assessed during the construction of our models.

Continuous variables were analysed as such. Predictors were selected using bootstrapped backward selection by multivariable fractional polynomial modelling.[17] Variables were selected if the mean bootstrap inclusion fraction (BIF) exceeded 66.7% out of 1000 bootstrapped replications across the 10 imputed data set.

Three models were constructed a priori, based on: (1) history, (2) history+spirometry and (3) history+spirometry+FeNO, using logistic regression analysis. For the history-only model, only those candidate predictors were assessed that are usually available for practitioners from history-taking and/or the medical record (items 1–4 and 5–14, table 1). The coefficients of the predictors were corrected for overoptimistic predictions by multiplying them by a fixed heuristic shrinkage factor[18] (see details in online supplementary appendix I). To facilitate clinical application of the model, we developed a risk score, based on the regression coefficients.[19]

Performance of the model

The predictive performance of the prediction model was assessed for discrimination, by calculating the area under the receiver operating characteristic curve (AUROC) and for calibration (goodness-of-fit), by drawing calibration plots and the Hosmer–Lemeshow (HL) test.[20] In addition, we calculated the 10th, 50th and 90th centiles of the distribution of predicted probabilities. The effect of addition of spirometry and subsequently FeNO to the history model was assessed by net reclassification improvement (NRI)[20] (see details in online supplementary appendix I). The three models were validated externally in the Unbiased BIOmarkers in PREDiction of respiratory disease outcomes (U-BIOPRED) data set (n=504)[21] (details in online supplementary appendix I). All statistical analyses were carried out in Stata/SE V.13.1 (Stata, College Station, Texas, USA).

RESULTS

Cohort

Data of 611 patients were analysed. Baseline patient characteristics (table 2) demonstrated a population with, on average, normal lung function (mean prebronchodilator FEV1 91.3% predicted; SD 15.4) and a low level of symptoms (mean ACQ-5 score 1.01; SD 0.95). However, the large SDs and wide ranges observed in baseline characteristics reflected a suitably heterogeneous asthma population. Eighty patients (13.1%) experienced one or more severe exacerbations during 12 months follow-up; a minimum of five events per variable modelled was therefore available.[22] Marked differences were seen at baseline between patients with and without exacerbations in use of long-acting β2-agonists, overuse of short-acting β2-agonists, previous asthma hospitalisation and having experienced an exacerbation in the previous year. All correlations between candidate predictors were below 0.7, reducing the chance of collinearity.

[TABLE 2] [TABLE 3]

Prediction models

The variables selected in the first model (history only) were: ACQ-5 score, current smoking, chronic sinusitis, previous hospitalisation for asthma and treatment with a course of oral corticosteroids in the previous year (table 3; see online supplementary appendix II table A1). The AUROC was 0.77 (95% CI 0.75 to 0.80; figure 1A). Predicted and actual risks were in agreement for the history-based model (figure 2, panel
1A), with the HL test yielding no indication of a poor fit (p value 0.35).
In the second model, addition of spirometry to the history model (table 3) increased the AUROC to 0.79 (95% CI 0.77 to 0.81) (figure 1A); calibration improved slightly (figure 2, panel 2A), HL test p value 0.54.
The third model, with FeNO added to the second model (table 3) changed the AUROC to 0.80 (95% CI 0.78 to 0.81; figure 1A) with a similar calibration (figure 2, panel 3A), HL test p value 0.44. The 10th, 50th (median) and 90th centiles of the distribution of the predicted probabilities are shown in the online supplementary appendix table A2, figure A1 appendix II). NRI tended to favour addition of spirometry to the history model (total NRI 0.094 for the patients with exacerbations with cut-off 50%; when adding FeNO to the model with spirometry, there was little reclassification (see online supplementary table A3 appendix II)). To improve applicability we checked in the first (history only) model whether ACQ-5 and ACQ-6 (ACQ-5 plus short-acting β2-agonist use frequency) could be exchanged. Similarly, we checked the exchangeability of prebronchodilator and postbronchodilator FEV1% predicted in the second model (with spirometry added). Predictive properties of the models remained virtually identical with the exchanged predictors. In the score system for both the history and history+spirometry models (table 4), higher scores indicated increased risk for a severe exacerbation over the next 12 months (figure 3; see online supplementary table A4 appendix II).

External validation

U-BIOPRED participants had poor asthma symptom control and low lung function; 55.6% had an asthma exacerbation in the previous year (see online supplementary table A5 appendix II). The exacerbation risk was higher than in the derivation data set, with 34.9% experiencing a severe exacerbation during 1 year follow-up. Discriminative properties of the models were lower in the external validation set (AUROC 0.72 (95% CI 0.70 to 0.73), 0.72 (95% CI 0.71 to 0.74) and 0.72 (95% CI 0.71 to 0.73)) for the three models, respectively (figure 1B).
The calibration of the history model demonstrated evident underestimation (circles above the line) in the first seven deciles (relatively low risk groups). Nevertheless, in the models with history+spirometry and history+spirometry+FeNO added, the calibration in lower-risk deciles was better, but in the upper four deciles (predicted probabilities >60%), predicted probabilities
were higher than observed risk (HL test for all models <0.05; figure 2, panels 1B–3B).

[FIGURE 1] [FIGURE 2] [TABLE 4]

DISCUSSION

The aim of this study was to develop a clinically relevant prediction model to calculate the probability that a patient with asthma will experience a severe exacerbation during the following year. A model with five easily accessible variables (ACQ-5 score, self-reported current smoking, self-reported chronic sinusitis, previous admission for asthma and a severe exacerbation in the previous year) added with prebronchodilator FEV1% predicted performed well on external validation. The addition of FeNO to this model did not improve predictive performance.

This study confirms and extends previous studies[6 11] showing that a previous exacerbation is among the strongest predictor for future exacerbations. With the exception of self-reported chronic sinusitis, the other predictors in our model also belong among the variables most frequently reported to be associated with risk of exacerbations. Each of the predictors in our model (except chronic sinusitis) was also identified in previously published models, such as the TENOR risk score (in severe asthma or difficult-to-treat asthma),[12] a risk score for exacerbations (from a clinical trial database in patients with ≥1 exacerbations in the previous year and suboptimal symptom control on treatment), [13] the severity of asthma score,[11] validated in patients with moderate to severe persistent asthma and the profile of asthma risk,[10] derived from a health maintenance organisation cohort with patients who had been hospitalised for asthma the previous 2 years or had received at least two dispensings of antiasthma medication in the year before recruitment. Measures of asthma control were included in all these four models whereas previous hospitalisations, recent exacerbations and spirometry measures occurred in three out of four models. Chronic sinusitis is associated with severe asthma,[23] but it has rarely been assessed as a predictor of exacerbations. The mechanism, if any, is still unknown although allergic triggers or nasal polyps may be involved.

[FIGURE 3]

Although ethnicity, age, gender and education level have been reported as predictors of exacerbations,[9 10 12] it is unlikely that demographic factors are as strong a predictor as clinical factors.

They were also not listed as risk factors for poor asthma outcomes by GINA[1]; they were therefore not assessed in our study.

Our study has several strengths: the ACCURATE trial had a pragmatic design, with few exclusion criteria. Patients were recruited in primary care and treatment by a pulmonary specialist was not an exclusion criterion. This population therefore reflects a broad, relatively unselected asthma population with considerable variability in the baseline patient characteristics, facilitating the development of a stable prediction model. The high level of completeness of data in a large (n>600) cohort, predictor selection by bootstrapping and application of shrinkage probably contributed to the preservation of good model performance on external validation in a different population with more severe asthma and a higher exacerbation risk.

The use of the standardised definition of the outcome variable (severe exacerbations by ATS/ERS criteria)[15] increases the interpretation[24] and applicability of this model in clinical practice.

The score system enables immediate application of the model in daily practice without using any resources.

Nevertheless, we acknowledge the following limitations. Since our model was developed using data from a randomised trial, treatment effects may have affected the predictions in two ways: either treatment could have been a predictor itself, or treatment could have interacted with other predictors. The first possibility was checked in an additional analysis. We found that treatment was not selected as a predictor when offered in addition to the history-based model (mean BIF 36.8). The latter possibility is less plausible: the treatment algorithms were targeted at different levels of asthma symptom control, based on ACQ score.

However, the candidate predictors we assessed were reported by GINA as predictors for exacerbations independent of symptoms.

Nevertheless, the repetitive application of each treatment algorithm could have reduced the predictive value particularly of ACQ and FeNO by preventing events happening (possibly introducing bias). Using repeated measurements of ACQ and FeNO in the model may have improved its predictive capacity. We chose not to do so because the collection of repeated measurements complicates clinical application.

A second limitation may be the limited number of exacerbations: some authors recommend a minimum of 10 events per predictor, however this criterion may be too conservative.[22] It also hampered any testing of interactions between predictors with sufficient statistical power. The third limitation is that our definition of an exacerbation was not identical to the definition as proposed by the ATS/ERS[15]: we could not verify whether patients visiting an emergency department and those hospitalised were treated with systemic corticosteroids.

Given the Dutch healthcare system, in which the general practitioners act as gatekeepers to secondary care, the protocol was based on the presumption that all patients visiting the emergency department and those hospitalised were treated with systemic corticosteroids. Finally, an important limitation is that the history model's calibration was lower on external validation in the U-BIOPRED data set, with exacerbation risk underestimated for many patients. Adding spirometry and FeNO values, however, improved the agreement of observed and predicted probabilities, except for some miscalibration overestimation when predicted risks exceeded 60%. Clinical consequences of this potential overestimation of risk are probably limited: most practitioners presumably will consider changing interventions at risks <60%.

To increase clinical applicability, and assess the added value of objective parameters separately, we built three models, based on: (1) history, (2) history+spirometry and (3) history+spirometry+ FeNO. The history-only model, which does not require any equipment, performed well on internal validation. However, on external validation, while discrimination remained high, calibration decreased substantially. In particular, predicted risks up to 25% were too low, which might lead to undertreatment if the model were applied to clinical practice. It should be noted, however, that this miscalibration was observed in a population quite different from the population the model was derived in: the U-BIOPRED population largely consists of patients with severe asthma and this is reflected in an annual exacerbation risk of about 35% against 13% in the ACCURATE cohort.

Additional validation studies in primary care populations may clarify the history model's performance in other primary care cohorts containing the necessary predictors and severe exacerbations as the outcome.

Adding spirometry to the history model resulted in a modest increase in predictive value and, more importantly, in considerable improvement of calibration in the external validation sample. The remaining miscalibration pertained to predicted risks of 60% and higher. However, these overestimations may not be important, as in clinical practice most physicians are likely to feel comfortable with intervening once the risk of severe exacerbation exceeds 50%, limiting potential overtreatment.
Although the use of spirometry presupposes equipment, training and time, it is currently considered to be part of standard asthma care,[1] so FEV1 values should be used additionally as a predictor when available. Moreover, since the last major revision of the GINA report in 2014, after diagnosing asthma, spirometry is recommended to be used primarily for risk assessment rather than for therapy adjustment.[25] We also considered FeNO as an additional predictor and as a surrogate for sputum or blood eosinophilia (which were not collected in this trial) even though the association is not strong.[26] The present data suggest that there is no added value of FeNO on top of history and spirometry to identify patients at risk for future severe exacerbations.
Both additions were assessed by NRI. Reclassification, using arbitrary prediction cut-offs for preventive action of 25% and 50%, also tended to favour adding spirometry values to the history model.
According to the GINA strategy report,[1] asthma control means not only good symptom control, but also control of future risk; both of these should be assessed periodically. The added value of the present risk score is that an individual risk for an exacerbation for the next 12 months can be calculated in a simple way. By combining information on the most important risk factors (as listed by GINA) practitioners gain information on future risks in a more explicit way: exacerbation risk in percentage (with 95% CI) rather than the mere presence or absence of risk factors in a particular patient. Moreover, it prevents practitioners from targeting solely at a single risk factor.
When targeting at for example recent exacerbations, a practitioner omits other relevant information. Notably, a model using solely recent exacerbations to predict future exacerbations yielded an AUROC of 0.66.
Although there are no criteria for the level of exacerbation risk that should prompt practitioners to take action, the score system shown in table 4, online supplementary table A3 and figure A2 (appendix II) may assist practitioners in making decisions based on the patients' individual risk. If a patient with good symptom control (ACQ<0.75) during a scheduled visit scores above a particular cut-off (eg, 6 points, corresponding to a predicted risk of nearly 20% of a severe exacerbation in the next 12 months), the practitioner may consider implementing risk reduction strategies such as providing a written action plan, assessing inhaler technique and adherence, increasing the frequency of review, removal of modifiable risk factors or increasing the treatment step. Conversely, given that many practitioners are not amenable to decreasing treatment steps,[27 28] our prediction model may also support such decreases, for example by a dose reduction when a patient with stable and well controlled asthma scores <3 points (corresponding to a risk of exacerbation of <9%).
After additional validation in different (first, second and third line care) clinical settings, studies in a day-to-day practice should point us how this score can assist practitioners in an optimal way (eg, as an app or automatically derived scoring

systems from the electronic patient record). The merits of this scoring system may be dependent on the healthcare system it is used in.

CONCLUSION

In a suitably heterogeneous primary care asthma population with a 13% chance of experiencing a severe exacerbation within the next year, we found that a simple prediction model containing five medical history items and spirometry identified patients at risk for an exacerbation in the coming year (AUROC 0.79). Predictive properties remained largely intact on external validation (AUROC 0.72) in a population with more severe asthma and a higher (35%) exacerbation risk. If validation in a suitable primary care data set yields similar findings, these models would merit an implementation study in clinical practice to assess their utility.

Correction notice

This article has been corrected since it was published Online First. Data in table 4 has been updated.

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RJBL, PJS, HKR and GtR contributed to the study protocol. RJBL, PJH, EHT, JBS-S, WJJA, TRJS, KFC, ARS, PJS, JKS and GtR contributed to the data acquisition of the ACCURATE trial; KFC, ARS and PJS contributed to the protocol and data acquisition of the U-BIOPRED study. RJBL and GtR analysed the data, PJS and HKR assisted on the interpretation. RJBL, PJS, HKR and GtR wrote the first draft of the manuscript. All authors critically revised the manuscript for intellectual content and approved the final version. RJBL and GtR had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis: RJBL and GtR act as guarantors.

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Competing interests

JBS-S holds stock in Grace Bros and has received consultancy fees from AstraZeneca, GlaxoSmithKline and Novartis, as well as grant funding from ACME Pharmaceutical. The institute of PJS has received a public– private grant by the Innovative Medicines Initiative covered by the European Union and the European Federation of Pharmaceutical Industries and Associations. KFC has received honoraria for participating in Advisory Board meetings regarding treatments for asthma and COPD for GSK, AZ, Novartis and J&J and has received grant funding through his institution from Pfizer, GSK and Merck. ARS is an employee and holds stock in GlaxoSmithKline. HKR has participated on advisory boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline and Novartis, is participating on a joint data monitoring committee for AstraZeneca, GlaxoSmithKline, Merck and Novartis, has provided consultancy services for AstraZeneca, has provided continuing medical education presentations at symposia funded by AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis and Teva and has received unconditional research funding from AstraZeneca and GlaxoSmithKline. HKR is Chair of the GINA Science Committee. JKS has received research grants from Boehringer Ingelheim, GlaxoSmithKline, Chiesi and Fonds NutsOhra (1101–081), as well as non-financial support from AstraZeneca (3.4.07.044).

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Provenance and peer review

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TABLES AND FIGURES

Table 1 Candidate variables for prediction of risk of asthma exacerbation based on Box2-2B of the GINA 2014 report and their operationalisation* for the predictor analysis

	Risk factor for exacerbations (GINA 2014)	Operationalisation in ACCURATE database
1	Uncontrolled asthma symptoms	Asthma Control Questionnaire (ACQ-5; continuous)
2	High SABA use	≥1 puff a day during the last 7 days before baseline
3	Inadequate ICS: not prescribed	No ICS prescribed at baseline
4	Inadequate ICS: poor adherence	Medication Adherence Rating Scale (continuous)
	Inadequate ICS: incorrect inhalation technique	Not available
5	Low FEV1	Prebronchodilator FEV1% predicted (continuous)
6	Major psychological problems	Self-reported use of antidepressants
7	Major socioeconomic problems	Income (ordinal)
8	Exposures: smoking	Current smoking
9	Exposures: allergen exposure if sensitised	Positive-specific IgE titres to house dust mite and/or grass and/or birch pollen† and/or IgE positivity to cat or dog combined with ownership
10	Co-morbidities: obesity	Body mass index (continuous)
11	Co-morbidities: rhinosinusitis	Self-reported complaints of chronic sinusitis
12	Co-morbidities: confirmed food allergy	Self-reported food allergy
	Pregnancy	Not available
	Sputum/blood eosinophilia	Not available
13	Ever intubated or intensive care	Self-reported hospitalisation (ever) for asthma
14	≥1 severe exacerbation in last 12 months	Self-reported steroid burst/hospital admission for asthma in the previous year

*Operationalisation of some variables differed from the GINA report; Fe_{NO} was also assessed in one of the models (values were analysed as dichotomous variables unless stated otherwise).
†Exposure to each of these allergens can be assumed in the Netherlands.
ACCURATE, Asthma Control Cost-Utility RAndomized Trial Evaluation; ICS, inhaled corticosteroids; SABA, short-acting β_2-agonist.

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Table 2 Baseline characteristics of the model derivation population*; bold variables are candidate predictors

	Patients without exacerbation (n=531)	Patients with exacerbation (n=80)	Total (n=611)	Observations n (%)
Sex % female	67.0	77.5	68.4	611 (100)
Mean age years (SD; range)	39.0 (9.2; 17–55)	42.1 (8.4; 18–51)	39.4 (9.1; 17–55)	611 (100)
Income (mode range in Euros)	>50.000	35.000–50.000	>50.000	592 (96.9)
Body mass index kg/m² (SD; range)	26.3 (5.3; 13.0–56.8)	26.8 (5.7; 17.4–41.9)	26.4 (5.4; 13.0–56.8)	590 (96.6)
Asthma duration years (SD; range)	18.0 (13.1; 0–51)	23.0 (13.4; 0–46)	18.6 (13.2; 0–51)	569 (93.1)
Current smokers %	12.2	26.6	14.1	605 (99.0)
Previous smokers %	31.9	40.4	32.9	591 (96.7)
Chronic sinusitis %	9.2	23.4	11.0	599 (98.0)
Atopy % total IgE >100 kU/mL	50.5	51.4	50.6	569 (93.1)
Self-reported food allergy %	14.3	15.8	14.5	593 (97.1)
Exposure to sensitised allergens	71.1	67.0	71.2	569 (93.1)
Self-reported antidepressants use %	5.7	8.8	6.1	611 (100)
ACQ-5 score (SD; range)	0.93 (0.86; 0.0–4.8)	1.57 (1.25; 0.0–5.6)	1.01 (0.95; 0.0–5.6)	593 (97.1)
Using inhaled corticosteroids %	80.9	89.7	82.1	592 (96.9)
Beclomethasone equivalent dose (SD; range)	773 (619; 0–4000)	1216 (794; 0–4000)	832 (662; 0–4000)	592 (96.9)
LABA use %	46.9	64.1	49.2	592 (96.9)
High SABA use ≥1 puff/day, %	26.8	47,4	29.5	593 (97.1)
Medication Adherence Rating Scale score (SD; range)	3.53 (0.55; 1.7–5)	3.58 (0.62; 1.6–4.6)	3.53 (0.56; 1.6–5)	593 (97.1)
Ever hospitalised for asthma %	10.3	21.6	11.7	588 (96.2)
Exacerbation previous year %†	7.7	39.7	11.8	600 (98.2)
FEV1% predicted (SD; range)	92.1 (15.1; 36.8–147.0)	85.5 (16.1; 46.0–120.0)	91.3 (15.4; 36.8–147)	588 (96.2)
Fe_{NO} ppb (SD; range)	25 (23; 5–228)	32 (48; 5–297)	26 (28; 5–297)	585 (95.7)

*Participants in the ACCURATE study;[14] data from the three original randomisation arms were combined for the present analysis.
†Defined as a course of oral corticosteroids in the previous year.
ACQ, Asthma Control Questionnaire; ACCURATE, Asthma Control Cost-Utility RAndomized Trial Evaluation; LABA, long-acting B_2-agonist; SABA, short-acting B_2-agonist.

Table 3 ORs and coefficients* of logistic prediction models for severe asthma exacerbations

	History		History+spirometry		History+spirometry+Fe_{NO}	
	OR(95% CI)	Coefficient	OR (95% CI)	Coefficient	OR (95% CI)	Coefficient
ACQ (per 0.5 score)	1.55 (1.22 to 1.98)	0.208	1.52 (1.19 to 1.94)	0.198	1.52 (1.19 to 1.94)	0.195
Current smoking	2.13 (1.08 to 4.17)	0.712	1.83 (0.93 to 3.62)	0.570	1.77 (0.89 to 3.50)	0.532
Chronic sinusitis	2.09 (1.02 to 4.28)	0.694	2.49 (1.17 to 5.31)	0.860	2.39 (1.11 to 5.14)	0.813
Ever admitted asthma	2.28 (1.16 to 4.49)	0.778	1.90 (0.95 to 3.82)	0.606	1.88 (0.94 to 3.79)	0.590
Oral steroids previous year	3.52 (1.68 to 7.36)	1.188	3.69 (1.74 to 7.80)	1.229	3.76 (1.79 to 7.94)	1.236
FEV1% predicted (per 10%)			0.97 (0.95 to 0.99)	−0.281	0.97 (0.95 to 0.99)	−0.270
Fe_{NO} (per 10 ppb)					1.01 (1.00 to 1.01)	0.059
Intercept		−4.595		−0.491		−0.737

*Coefficients of the models shown after shrinkage; shrinkage factors were 0.9440, 0.9407 and 0.9326 for the history, spirometry and Fe_{NO} model, respectively.
ACQ, Asthma Control Questionnaire.

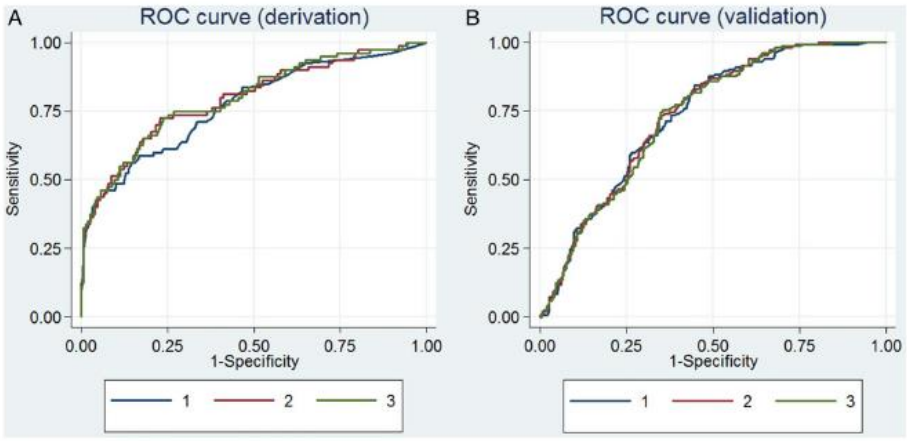

Figure 1 Receiver operating characteristic (ROC) discrimination curve for severe asthma exacerbation prediction models based on history (1), history+spirometry (2) and history+spirometry+FeNO (3); on panel A for the derivation (Asthma Control Cost-Utility RAndomized Trial Evaluation) cohort and on panel B for the validation (Unbiased BIOmarkers in PREDiction of respiratory disease outcomes) cohort.

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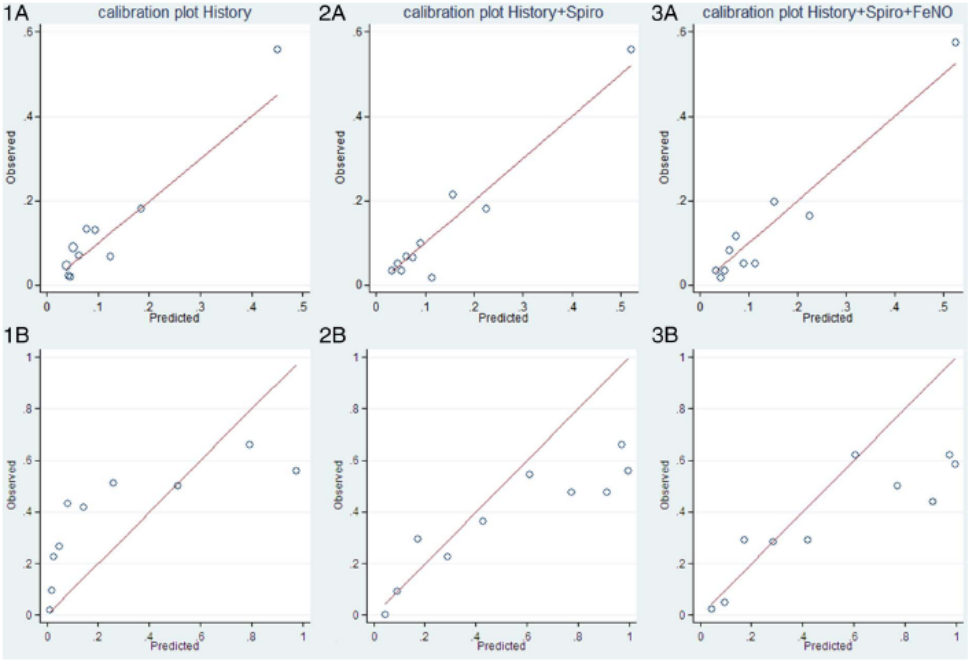

Figure 2 Calibration plots for models based on history (1A), history+spirometry (2A) and history+spirometry+Fe_{NO} (3A) in the derivation set shown in the upper three panels. Calibration plots in the validation data set are shown in the lower three panels (1B, 2B and 3B, respectively). On the x-axis the probability as predicted by the model, on the y-axis the probabilities as observed in the data. Circles represent mean predicted probabilities in 10 deciles; the closer the circles are to the straight line, the closer the predicted probabilities from the model are in agreement with the observed probability in the data set.

Table 4 Construction of the asthma risk score for the history and history+spirometry model.

		Points	
Factor		**History**	**History+spirometry**
ACQ score	<0.75	0	0
	0.75–1.50	1	1
	>1.5	4	4
Current smoking	No	0	0
	Yes	3	2.5
Chronic sinusitis	No	0	0
	Yes	3	3.5
Ever admitted for asthma?	No	0	0
	Yes	3	2.5
Steroids previous year?	No	0	0
	Yes	5	5
Spirometry (% predicted)	>90		0
	80–90		0.25
	<80		0.50
Total score (range)		0–18	0–18

ACQ, Asthma Control Questionnaire.

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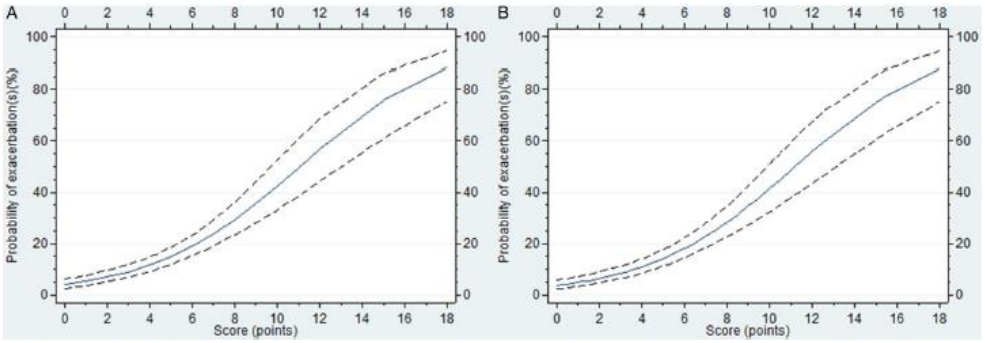

Figure 3 Predicted probabilities of at least one exacerbation during the next 12 months (y-axis) versus the points accredited by the score system (x-axis) for the history model (1) and history+spirometry model (2).