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1 **Detecting asthma exacerbations using daily home monitoring and machine learning**

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32 to publish.

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50 **Abstract**

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52 **Objective**

53 Acute exacerbations contribute significantly to the morbidity of asthma. Recent studies have
54 shown that early detection and treatment of asthma exacerbations leads to improved
55 outcomes. We aimed to develop a machine learning algorithm to detect severe asthma
56 exacerbations using easily available daily monitoring data.

57

58 **Methods**

59 We analysed daily peak expiratory flow and symptom scores recorded by participants in the
60 SAKURA study (NCT00839800), an international multicentre randomised controlled trial
61 comparing budesonide/formoterol as maintenance and reliever therapy versus
62 budesonide/formoterol maintenance plus terbutaline as reliever, in adults with persistent
63 asthma. The dataset consisted of 728,535 records of daily monitoring data in 2010 patients,
64 with 576 severe exacerbation events. Data post-processing techniques included
65 normalisation, standardisation, calculation of differences or slopes over time and the use of
66 smoothing filters. Principal components analysis was used to reduce the large number of
67 derived variables to a smaller number of linearly independent components. Logistic
68 regression, decision tree, naïve Bayes, and perceptron algorithms were evaluated. Model
69 accuracy was assessed using stratified cross-validation. The primary outcome was the
70 detection of exacerbations on the same day or up to three days in the future.

71

72 **Results**

73 The best model used logistic regression with input variables derived from post-processed data
74 using principal components analysis. This had an area under the receiver operating

75 characteristic curve of 0.85, with a sensitivity of 90% and specificity of 83% for severe
76 asthma exacerbations.

77

78 **Conclusion**

79 Asthma exacerbations may be detected using machine learning algorithms applied to daily
80 self-monitoring of peak expiratory flow and asthma symptoms.

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84 Key words: asthma; exacerbation; peak expiratory flow; home monitoring; machine learning

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86 Running title: Asthma exacerbations and home monitoring

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100 **Introduction**

101 Acute exacerbations of asthma are episodes of deteriorating symptoms, often with
102 concomitant reductions in lung function, requiring a change in treatment such as a short
103 course of oral corticosteroids¹. Acute exacerbations are an important cause of morbidity in
104 patients with asthma, and can result in days off work or school, hospital admission, or even
105 death. Preventing exacerbations is a key priority in the management of asthma². Regular use
106 of inhaled corticosteroids at an appropriate dose and with correct technique is the mainstay of
107 preventative asthma treatment, but does not completely eliminate exacerbations³.

108

109 The concept of detecting exacerbations at an early stage of development in order to intervene
110 and avert them has recently gained ground. McKeever *et al* showed that a self-management
111 plan which involved quadrupling the dose of inhaled corticosteroids at the first signs of an
112 asthma exacerbation (increased symptoms and/or reduced peak expiratory flow [PEF])
113 reduced exacerbation rates compared to standard treatment⁴. The typical changes in peak
114 expiratory flow and asthma symptom scores leading up to asthma exacerbations were initially
115 described by Tattersfield *et al*⁵. These authors showed that PEF began to gradually fall
116 approximately 10 days prior to an exacerbation, followed by a much steeper fall from 3 days
117 prior to an exacerbation, culminating in a 15-20% fall from baseline on the day of
118 exacerbation. Asthma symptom scores followed a very similar pattern, with a gradual rise
119 starting from 10 days prior to an exacerbation, followed by a steeper rise from 3 days prior to
120 an exacerbation. These results suggest that detecting asthma exacerbations up to three days in
121 advance using daily monitoring of PEF and symptoms is potentially feasible. Since then, a
122 number of researchers have investigated the sensitivity and specificity of algorithms based
123 upon daily electronic monitoring of symptoms and PEF to detect impending asthma
124 exacerbations^{6,7}. These studies used fairly simple statistical cut-offs for PEF and symptom

125 scores to detect exacerbation events, and moreover the datasets used were relatively small,
126 thus precluding more complex analyses such as examining temporal trends.

127

128 Machine learning is a branch of artificial intelligence in which statistical models are used to
129 learn patterns from data in order to accomplish a specific task. Applications of machine
130 learning within respiratory and other branches of medicine have grown significantly during
131 the past five years⁸. The most common applications are those in which cases are classified
132 into a small number of categories such as ‘low-risk’ and ‘high-risk’. Although machine
133 learning models have the potential to be more accurate than simpler predictive tools, their
134 complexity means that they require large training datasets of labelled cases for their
135 development.

136

137 The use of machine learning techniques to predict asthma exacerbations based on daily PEF
138 and symptom monitoring has been investigated in one previous study by Finkelstein *et al*⁹.
139 These authors utilised a moderately sized dataset of 7001 records submitted by adults with
140 asthma using home telemonitoring software. They investigated the predictive value of three
141 machine learning algorithms, namely naïve Bayesian classifier, adaptive Bayesian network,
142 and support vector machine. However, it should be noted that exacerbations in this study
143 were not defined as clinician-diagnosed events requiring treatment, but were instead based on
144 ‘alert levels’ defined using the home telemonitoring data itself.

145

146 We hypothesised that a predictive algorithm derived using machine learning techniques in
147 conjunction with a large training dataset of daily monitoring data would provide superior
148 accuracy for detecting asthma exacerbations compared to previously published models.

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150

151 **Methods**

152

153 Study dataset

154 We utilised a large dataset of daily PEF and symptom scores which were recorded by
155 participants in the SAKURA study (NCT00839800), an international multicentre randomised
156 controlled trial comparing budesonide/formoterol as maintenance and reliever therapy versus
157 budesonide/formoterol maintenance plus terbutaline as reliever, in patients age ≥ 16 years
158 with persistent asthma¹⁰. Eligibility criteria included a documented history of persistent
159 asthma for at least 6 months, reversible airway obstruction (increase in forced expiratory
160 volume in one second [FEV₁] of at least 12% relative to baseline with administration of a
161 bronchodilator), use of maintenance inhaled corticosteroids (ICS) for at least 3 months before
162 study entry, and having at least one asthma exacerbation in the 12 months prior to study
163 entry. Current or previous smokers with a smoking history of ≥ 10 pack years were excluded.
164 The study population had a mean age of 46 years with 68% being female. The mean
165 beclometasone dipropionate equivalent ICS dose at study entry was 1023 $\mu\text{g}/\text{day}$, and 62% of
166 patients were using long-acting β_2 agonists at study entry. The mean baseline FEV₁ was 70%
167 predicted, with mean reversibility following administration of a bronchodilator of 23%.

168

169 Participants in this study kept a paper diary in which they recorded on a daily basis:

170

- 171 i) PEF twice daily (best of three blows each time)
- 172 ii) Morning symptoms on an integer scale from 0 (no symptoms) to 3 (severe symptoms)
- 173 iii) Evening symptoms on an integer scale from 0 (no symptoms) to 3 (severe symptoms)
- 174 iv) Number of puffs of reliever inhaler taken overnight

- 175 v) Number of puffs of reliever inhaler taken during the day
176 vi) Whether or not they had woken up due to asthma during the previous night

177

178 These data were entered into an electronic database together with a record of days in which a
179 severe asthma exacerbation occurred. Severe exacerbations were defined as deterioration in
180 asthma leading to oral corticosteroid treatment for at least 3 days, or hospitalisation or
181 emergency room treatment due to asthma. Access to the dataset was provided to the
182 investigators by AstraZeneca using a secure online data repository and analysis platform.
183 Participants in the study gave informed consent for the secondary use of anonymised study
184 data for research.

185

186 Data analysis

187 The dataset consisted of 728,535 records of daily monitoring data in 2010 patients, with a
188 total of 576 severe exacerbation events. The mean length of follow-up for each patient was
189 362 days. The primary goal of the analysis was to derive and validate a predictive model
190 which could detect exacerbation events occurring on the same day or up to three days in the
191 future. The analysis consisted of a number of steps as described in the text below and
192 summarised in Figure 1. At each stage of the analysis a number of options were available,
193 each of which was systematically investigated. Once the most favourable option had been
194 selected this was then used for the remainder of the analysis until the final model was
195 reached. This process is described in the results section. Further details of the analysis
196 techniques are given in the Online Supplement.

197

198 *Processing of daily monitoring variables*

199 The nine basic daily monitoring variables entered into the predictive models were:

- 200 i) Morning, evening and mean peak expiratory flow rate.
- 201 ii) Morning and evening symptom scores
- 202 iii) Number of puffs of reliever inhaler used during the overnight and daytime periods
- 203 iv) Total of morning and evening symptom scores, and overnight and daytime reliever
- 204 inhaler usage
- 205 v) Waking during the previous night (yes/no)

206

207 We utilised a number of variable post-processing techniques, alone or in combination,

208 resulting in a total of 432 basic and derived variables:

- 209 i) Normalisation of variables as a percentage of the mean value for that patient
- 210 (normalisation), or as the number of standard deviations above or below the mean for
- 211 that patient (standardisation)¹³. The rationale for this is that some parameters
- 212 (particularly PEF) are heavily dependent on demographic characteristics such as age,
- 213 sex and height. Therefore it is logical to standardise values according to the mean
- 214 value for each individual, thus accentuating within-person rather than between-person
- 215 variability.
- 216 ii) Calculating the difference or the slope between the current value and the value
- 217 observed 1, 2, 3, 4 or 5 days ago, as an indication of the short-term trend. We chose to
- 218 explore this method since previous evidence has shown that exacerbations are often
- 219 preceded by short-term reductions in PEF and increases in symptom scores⁵.
- 220 iii) Applying filters in order to smooth short-term variability¹⁴⁻¹⁶. These were used since a
- 221 number of home monitoring measurements (particularly PEF) exhibit a degree of
- 222 random variability which may mask the underlying trend. Figure 2 shows an example
- 223 of PEF data before and after application of a smoothing filter.

224

225 *Variable selection and reduction*

226 As the total number of basic and derived variables (432) is very large and it is unclear which
227 of them are most predictive of exacerbations, both recursive feature elimination and principal
228 component analysis (PCA)¹⁷ were investigated as variable selection and reduction techniques.
229 Recursive feature elimination is a variable selection method which is used in combination
230 with a particular machine learning model and with cross-validation. Starting with the full list
231 of 432 variables, the weakest (least predictive) variables are eliminated from the model one
232 by one until the optimal sensitivity is reached. PCA is a data reduction method that is used to
233 reduce a large number of variables into a smaller number of linearly independent
234 (uncorrelated) components, each of which is a weighted linear combination of one or more of
235 the original variables. The purpose of PCA is to capture the variance or information content
236 of a dataset with many variables using a smaller number of components, which can then be
237 entered into predictive models. Since the components derived using PCA are linearly
238 independent (uncorrelated) they are more likely to have independent value when entered into
239 a predictive model. The numbers of components can be specified *a priori*. We investigated
240 PCA using 3, 5, 9, 20, 40, 60, 80 and 100 components. It should be noted that PCA is a
241 standalone procedure which occurs prior to entering data into a machine learning model,
242 whereas recursive feature elimination is integrated into the process of tuning and testing a
243 machine learning model.

244

245 *Application of class imbalance learning techniques*

246 Predicting asthma exacerbations from this dataset was a class imbalanced learning problem¹¹,
247 in which there were much fewer examples of exacerbation cases (approximately 0.08%) than
248 non-exacerbation cases (approximately 99.92%) in the dataset. Therefore, we investigated
249 class imbalance learning techniques that operate by resampling the training data. These

250 techniques increase the proportion of the training set that represents the minority
251 (exacerbation) class, aiming at producing models that are able to better recognise cases of the
252 minority class. Importantly, it should be noted that these techniques were only applied to the
253 training data, not the validation data from which the final model accuracy was determined.
254 The following three techniques were investigated:

- 255 i) Random under-sampling: Randomly discarding training data from the majority (non-
256 exacerbation) class.
- 257 ii) Random over-sampling: Randomly duplicating training data from the minority
258 (exacerbation) class.
- 259 iii) Synthetic minority over-sampling technique (SMOTE): Adding synthetic training data
260 that have been generated from the minority (exacerbation) class^{11,12}.

261 For each of these techniques we investigated different ratios of exacerbation to non-
262 exacerbation training data to determine which produced the best balance between sensitivity
263 and specificity.

264

265 *Development and validation of machine learning models*

266 We investigated a number of machine learning models:

- 267 i) Logistic regression: Statistical model in which the log odds of an event are assumed to
268 be linearly related to one or more predictor variables.
- 269 ii) Naïve Bayes: Conditional probability model in which the probability of an event is
270 assumed to be related independently to one or more predictor variables.
- 271 iii) Decision tree: Classification algorithm which assigns a category in a hierarchical
272 manner based upon decision points with respect to the predictor variables.
- 273 iv) Perceptron: Classification algorithm which assigns a category based upon whether a
274 weighted combination of the predictor variables exceeds a particular threshold.

275 The ability of the machine learning models to recognise exacerbation and non-exacerbation
276 cases was evaluated using sensitivity, specificity, and area under the receiver operating
277 characteristic curve (AUC). Sensitivity was defined as the true positive rate. We considered a
278 prediction to be a true positive if an exacerbation occurred on the same day or up to 3 days
279 after the prediction. Specificity was defined as the true negative rate. AUC was the area under
280 the curve formed by true positive and false positive rates obtained by varying the decision
281 thresholds within the machine learning models. We used stratified cross-validation¹⁸ to
282 evaluate each of the machine learning models. This procedure was chosen due to the small
283 number of exacerbation examples in the data set. It separates the data into k folds. $k-1$ folds
284 are used to train a predictive model, and the remaining fold is used for evaluation purposes.
285 In this study we used $k=5$ folds and for most analyses repeated the procedure 10 times. The
286 average sensitivity, specificity and AUC was calculated across the 10 repetitions (if
287 applicable).

288

289

290 **Results**

291 Qualitative examination of the dataset revealed that when all 576 exacerbation events were
292 taken in aggregate, each of the raw daily monitoring variables displayed a distinct pattern in
293 the run-up to exacerbation events, as shown in Figure 3. However, there was a great deal of
294 individual variability, meaning that none of these variables alone was sufficient to predict
295 asthma exacerbations with high sensitivity or specificity.

296

297 Developing a predictive model of asthma exacerbations presented a number of options at
298 each step such as the choice of variable processing techniques, variable selection method,

299 class imbalance learning technique and machine learning model. These choices were made
300 sequentially until the final model was reached, as described below.

301

302 *i) Exploratory analysis of variable processing methods*

303 We initially investigated the effect of different variable processing techniques on the
304 predictive ability of home monitoring variables. For this part of the study, three basic
305 variables were used (mean PEF, total symptom score and night-time waking), entered into a
306 logistic regression model with the use of SMOTE to address class imbalance. Results were
307 assessed using 5-fold cross-validation repeated 10 times. Table S1 in the Online Supplement
308 shows the predictive performance of the basic variables compared to when smoothing filters
309 were applied. When applied alone the smoothing filters did not confer an advantage
310 compared to the basic variables. The best performing filter was Savitzky-Golay with window
311 width $s=3$ and polynomial order $d=2$, so this was retained for subsequent analyses.

312

313 Table S2 shows the performance of standardised and normalised variables, with and without
314 the additional use of the Savitzky-Golay smoothing filter. Standardised variables are
315 expressed as the number of standard deviations above or below the mean value for that
316 patient, while normalised variables are expressed as the percentage of the mean value for that
317 patient. Standardisation improved the predictions compared to the basic variables whereas
318 normalisation worsened them. Therefore, only standardisation was retained as a variable
319 processing method for subsequent analyses.

320

321 Table S3 shows the performance of differenced measurements and slope (over 1 to 5 days),
322 with and without the additional use of standardisation and Savitzky-Golay filter. For each of
323 these tests, a total of 15 processed variables were entered into the model, since the difference

324 or slope was calculated over a period of 1, 2, 3, 4 or 5 days for each of the three basic
325 variables. It was observed that differenced values were moderately sensitive and specific,
326 whereas slopes were more sensitive but rather non-specific. Both variable processing
327 methods were retained for future analyses.

328

329 *ii) Comparison of machine learning algorithms*

330 In light of the exploratory analysis described in the previous section, a list of predictor
331 variables was chosen in order to test the four machine learning models (logistic regression,
332 naïve Bayes, decision tree and perceptron). These were the three basic variables used in the
333 previous section (mean PEF, total symptom score and night-time waking) smoothed using the
334 Savitzky-Golay filter, with standardisation, or with differencing (over 1, 2, 3, 4 or 5 days), or
335 with calculation of the slope (over 1, 2, 3, 4 or 5 days). These analyses were performed using
336 SMOTE to address class imbalance, and a grid search to tune parameters based on one run of
337 5-fold stratified cross-validation for each combination of parameter values investigated.
338 Table S4 shows the parameter values investigated and the performance obtained by each of
339 the machine learning models using these input data. Logistic regression gave the best balance
340 between sensitivity and specificity and was therefore used in subsequent analyses.

341

342 *iii) Comparison of class imbalance learning techniques*

343 We found that using over-sampling, under-sampling or SMOTE was essential to overcome
344 the class imbalance problem and enable the logistic regression algorithm to recognise
345 exacerbation cases. Table S5 shows the results obtained by logistic regression using no
346 resampling and using different class imbalance learning techniques. These analyses were
347 performed with 5-fold cross-validation repeated 10 times. The most balanced results in terms
348 of sensitivity and specificity were provided with a 1:1 ratio of exacerbation and non-

349 exacerbation cases. The three class imbalance learning techniques performed equally with
350 respect to sensitivity and specificity when using a 1:1 ratio of exacerbation and non-
351 exacerbation cases. For subsequent analyses under-sampling was used since this was the
352 simplest and least computationally intensive option.

353

354 *iv) Comparison of variable selection and data reduction techniques*

355 In order to develop and validate the final predictive model, the variable processing techniques
356 detailed in section (i) above were applied alone or in combination to the full list of nine raw
357 monitoring variables to produce a total of 432 raw and processed variables. The final model
358 used logistic regression as the machine learning model with under-sampling as the class
359 imbalance technique. Recursive feature elimination and PCA were applied as described in the
360 Methods section, with the results shown in Table S6. These analyses were performed with 5-
361 fold cross-validation repeated 10 times. PCA with the number of components (c) = 80
362 achieved the best overall results, with sensitivity of 90% and specificity of 83% for asthma
363 exacerbations, and an AUC of 85%, as shown in Figure 4.

364

365

366 **Discussion**

367 We have shown that machine learning techniques in combination with simple daily
368 monitoring data such as PEF and patient-reported symptom scores can predict asthma
369 exacerbations with good sensitivity and specificity. In particular our best algorithm, using
370 logistic regression in combination with PCA for feature extraction, achieved sensitivity of
371 90% and specificity of 83% for asthma exacerbations, with an AUC of 85%. This was
372 achieved using class imbalance techniques to better balance the positive and negative training
373 data, enabling the resulting models to better recognise minority cases. This was necessary due

374 to the severe class imbalance in the original dataset (0.08% exacerbation cases, 99.92% non-
375 exacerbation cases). Without using class imbalance learning techniques, most statistical and
376 machine learning models would simply predict all cases as being in the majority class (ie.
377 non-exacerbation cases) since this would yield an accuracy of 99.92% - however, such a
378 model would clearly not have clinical utility. Therefore, class imbalance learning techniques
379 are essential to develop predictive models that give meaningful results. It should be noted that
380 class imbalance techniques were only used to balance cases in the training data, not the
381 validation data. Therefore the sensitivity, specificity and AUC values we have reported are
382 applicable to prospectively collected home monitoring data. Using predictive models in
383 clinical practice requires consideration of additional factors such as the relative ‘cost’ of false
384 negative and false positive results. For instance it may be decided that a given number of
385 false alarms will be tolerated to correctly diagnose one exacerbation event. This will
386 determine the threshold of the model output that is chosen to initiate further action such as
387 contact with a health professional.

388

389 The primary outcome of this study was the accuracy of predicting asthma exacerbations
390 occurring on the same day or up to 3 days in the future. This was chosen based on previous
391 work by Tattersfield *et al* showing that significant changes in PEF and asthma symptoms start
392 to occur 3 days prior to exacerbations⁵. Given that the anti-inflammatory actions of inhaled
393 and oral corticosteroids commence within 2-3 days and 3-8 hours of administration
394 respectively^{19,20}, intervention within this timeframe would be expected to have a favourable
395 effect, potentially averting incipient exacerbations before they become severe. McKeever *et*
396 *al* showed that a strategy of quadrupling inhaled corticosteroid dose in response to a drop in
397 PEF or increase in asthma symptoms had the effect of reducing asthma exacerbations⁴. It is

398 likely that improving the algorithm for early detection of exacerbations would further
399 enhance the efficacy of this strategy.

400

401 A number of smartphone apps already exist for daily monitoring and self-management of
402 asthma²¹. The algorithms we have developed could be readily incorporated into a smartphone
403 app, providing patients and clinicians with an early warning of impending exacerbations.
404 Although development of machine learning models is often computationally intensive due to
405 the need to tune the model to a large training dataset, applying the final model to new data is
406 usually much less so. The final model we generated uses relatively simple manipulations of
407 data which would be well within the capacity of modern smartphones.

408

409 Further treatment or management studies are needed to determine the best response to
410 algorithm-generated early warnings, with the goal of reducing severe exacerbations, use of
411 oral corticosteroids and hospital admissions. Potential options include contact with a
412 healthcare professional or a patient-initiated increase in therapy such as a quadrupling of
413 inhaled corticosteroid dose⁴. Moreover, the health economic benefits of such an approach
414 require evaluation, given the potential for false alarms and unnecessary healthcare contacts.

415

416 Strengths of our study include the use of a large international dataset, incorporating 728,535
417 patient-days of data in 2010 patients, with a total of 576 severe exacerbation events. We
418 investigated a wide variety of machine learning techniques in order to optimise the potential
419 of this dataset. However we acknowledge a number of potential limitations of the study. This
420 was a post hoc analysis of daily diary data that were collected as part of a randomised
421 controlled trial, and were not originally intended to be used for exacerbation prediction. The
422 data were collected using paper diaries which may have been prone to inaccurate transcribing

423 or fabrication. Moreover, there was no way of verifying correct technique with home peak
424 expiratory flow measurements. Electronic real-time data collection using a smartphone app
425 wirelessly linked to a digital spirometer with in-built quality control would have provided
426 more reliable data. It is also possible that the simple three-point symptom scores utilised in
427 this study were not maximally predictive. Validated daily outcome measures such as the
428 Asthma Control Diary²² and the Asthma Daily Symptom Diary²³ are available, but these
429 instruments are subject to licencing restrictions which prevent their free use on electronic
430 platforms. Reliever inhaler usage was self-reported in our study whereas there is now the
431 potential to objectively monitor this using digital inhaler attachments²⁴⁻²⁷. There is emerging
432 evidence that monitoring reliever inhaler usage in real time may provide important predictive
433 information. Objectively monitored reliever inhaler use has been shown to increase in the
434 days leading up to asthma exacerbations²⁶ and hospital admissions²⁷. It is possible that daily
435 monitoring of additional variables such as exhaled nitric oxide would also improve the
436 predictive power of home monitoring, albeit with the drawback of increasing cost and
437 complexity. Exhaled nitric oxide is a biomarker of steroid-responsive airway inflammation
438 which can be measured in a variety of settings²⁸. A recent systematic review and meta-
439 analysis has shown that tailoring asthma treatment based on exhaled nitric oxide
440 measurements can reduce exacerbations in both adults and children with asthma²⁹. Home
441 monitoring of exhaled nitric oxide using portable devices has been shown to be feasible by a
442 number of investigators³⁰⁻³⁴, and Van der Walk *et al* observed increases in exhaled nitric
443 oxide in the days leading up to moderate exacerbations in children with asthma³².

444

445 In conclusion, we have shown that machine learning algorithms have the potential to improve
446 the early detection of asthma exacerbations when compared to traditional paper-based action
447 plans. We anticipate that electronic data collection using smartphone apps linked to digital

448 spirometers and inhalers will further improve the predictive ability of these algorithms.
449 Further studies are needed to assess whether this can translate into improved clinical
450 outcomes, and whether asthma self-management using predictive algorithms is cost-effective.

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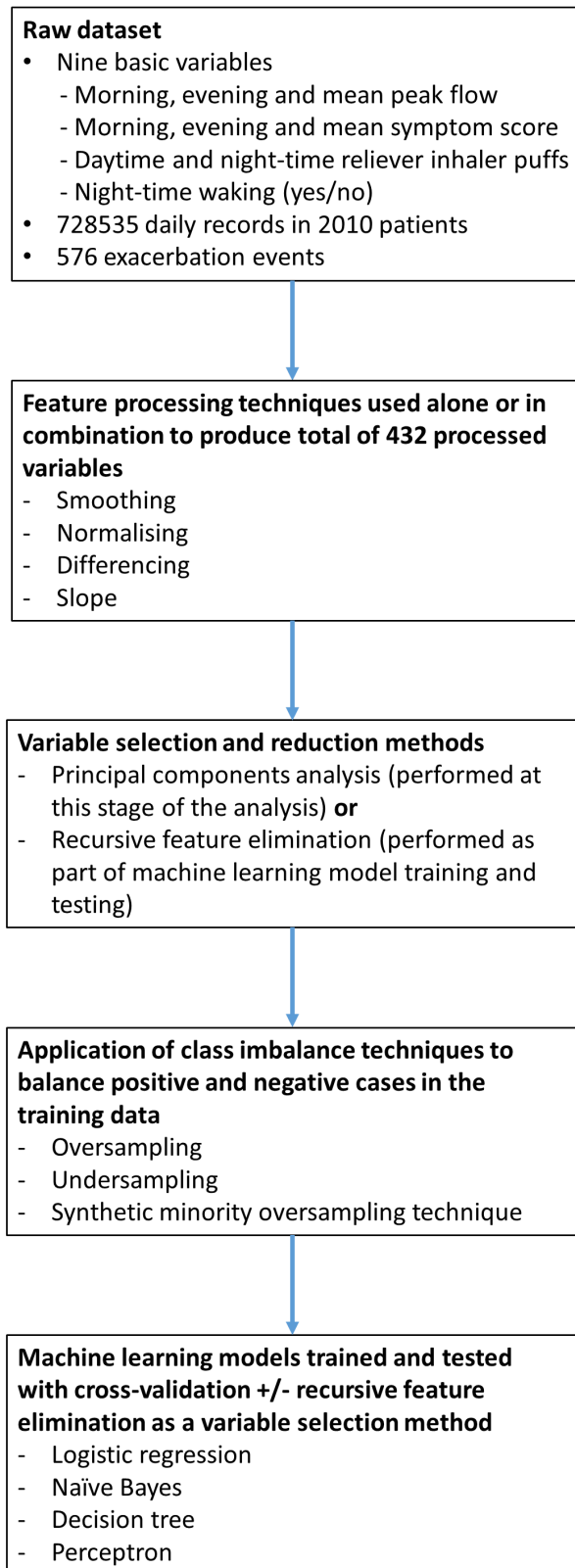
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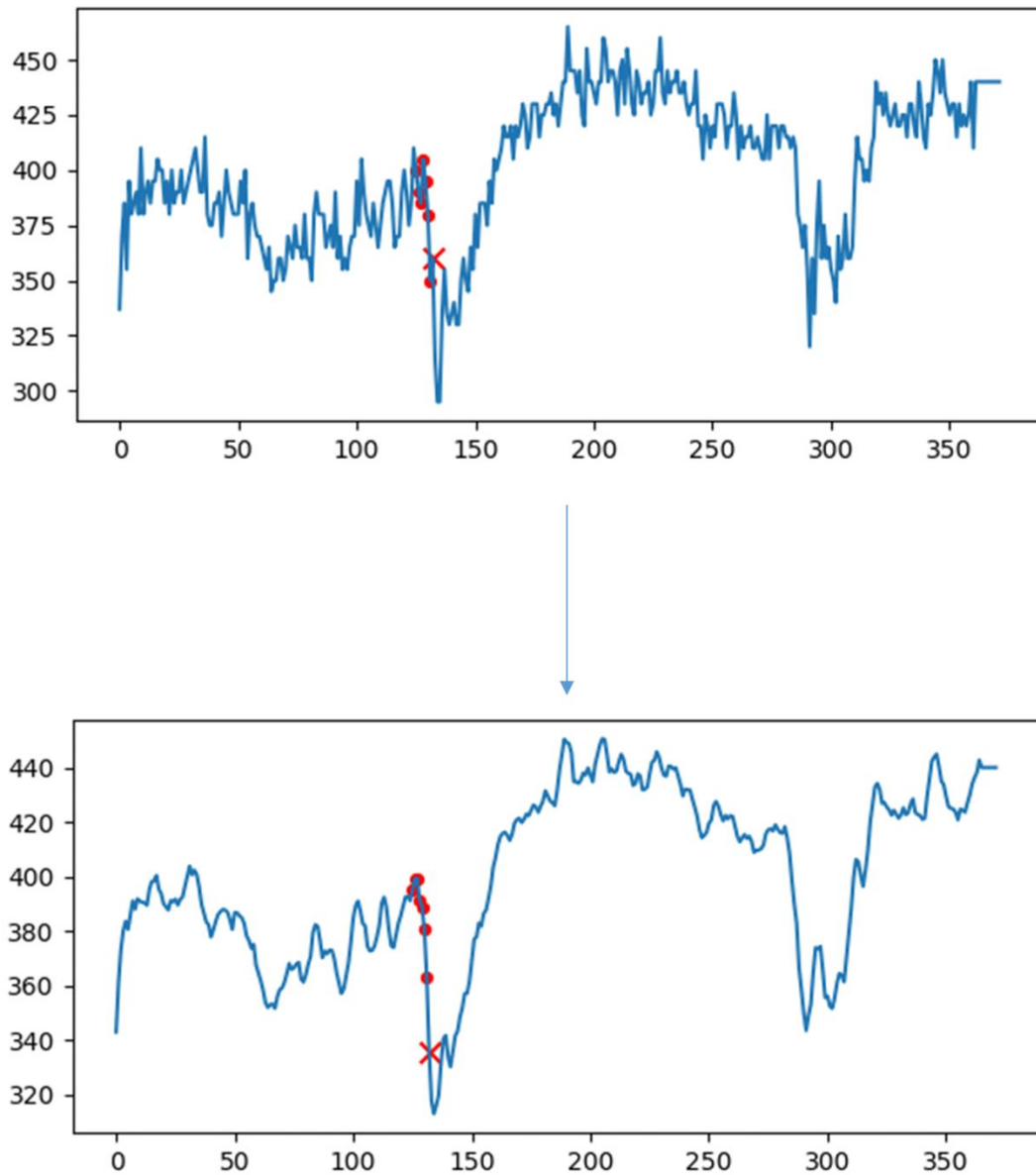
621 **Figure 1: Summary of data analysis steps**



623 **Figure 2: Application of a data smoothing filter**

624 Daily peak expiratory flow data (L/min) is shown before and after application of a Savitzky-

625 Golay filter.



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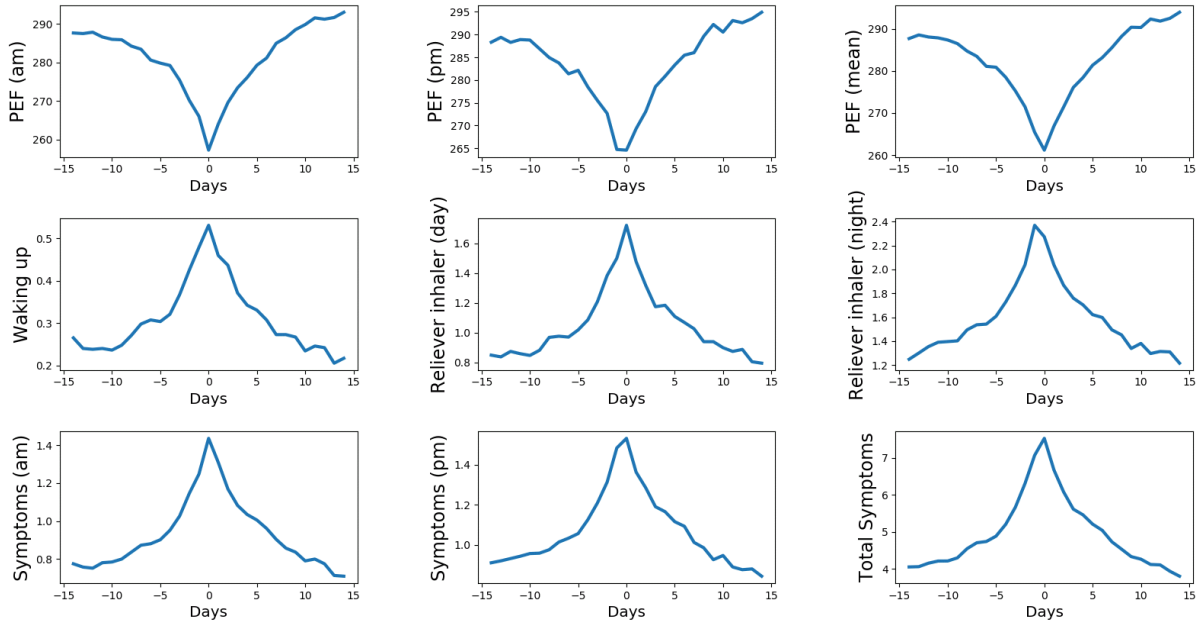
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631 **Figure 3: Changes in daily monitoring variables in the period preceding and following**
632 **exacerbations**

633 Panels show the average value of daily monitoring variables immediately preceding and
634 following exacerbation events occurring on Day 0. PEF = peak expiratory flow (L/min).



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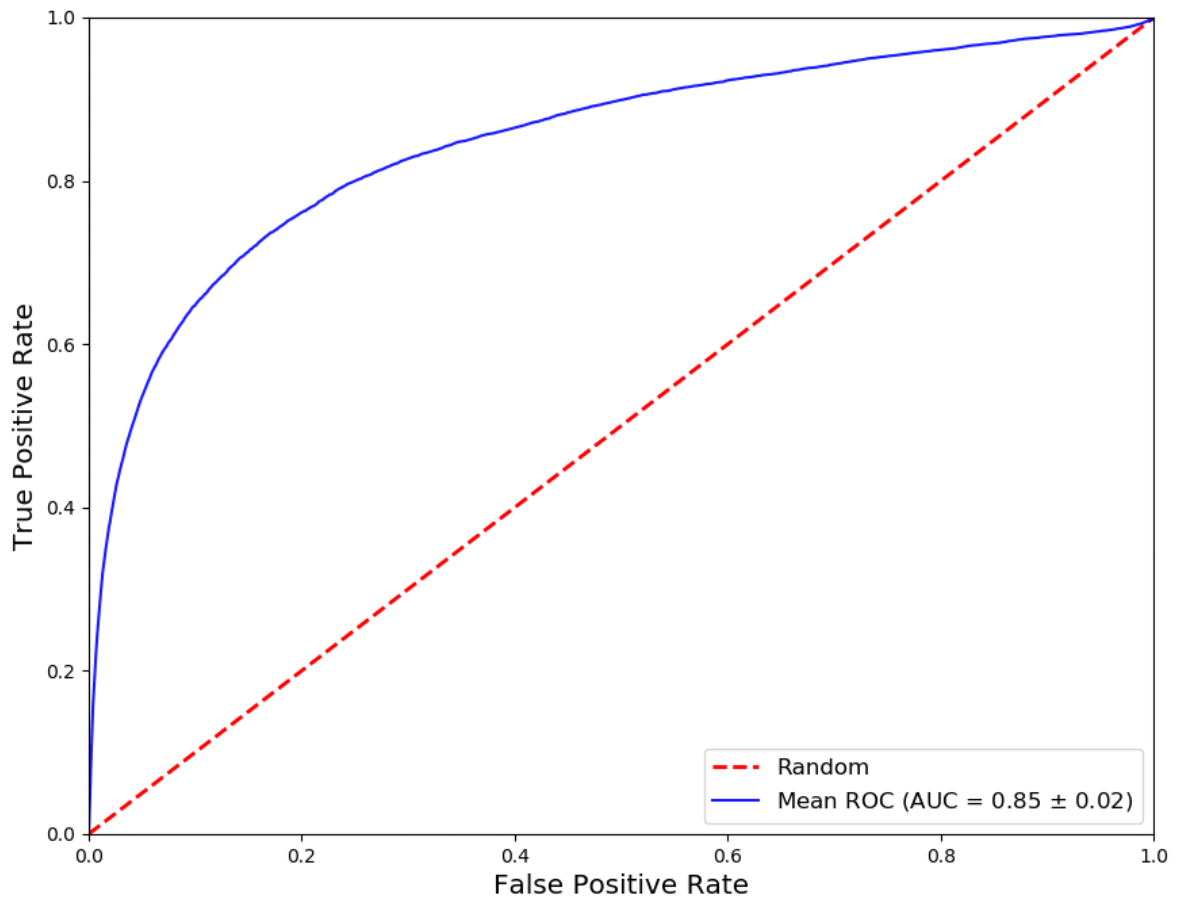
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647 **Figure 4: Receiver operating characteristic curve for the detection of asthma**
648 **exacerbation using the final logistic regression model**



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660 **Detecting asthma exacerbations using daily home monitoring and machine learning**

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664 **Supplementary methods and data**

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688 **Further details of post-processing techniques**

689 Filter techniques:

- 690 • Median Filter – this filter keeps a sliding window over the data produced over time
691 and uses the median value in this sliding window as a variable.
- 692 • Savitzky-Golay Filter – this filter fits a low order polynomial to the examples in a
693 sliding window of the data based on linear least squares.
- 694 • Wiener Filter – this filter uses Wiener deconvolution to smooth signals based on a
695 sliding window of the data.
- 696 • Median Filter, Savitzky-Golay Filter and Wiener Filter's parameter s refers to the
697 sliding window used for smoothing the data.
- 698 • Savitzky-Golay Filter's parameter d is the polynomial order used by the filter.

699

700 Difference and slope techniques:

- 701 • Difference refers to the difference between the current value of a monitored variable
702 and its value d days ago.
- 703 • Slope refers to the slope of the regression line that fits a sequence of values of the
704 variables. The sequence includes the current value and all values up to and including
705 d days ago.

706

707 Principal Component Analysis (PCA):

- 708 • PCA is a variable transformation technique that converts a set of values from possibly
709 correlated variables into a set of values of linearly uncorrelated variables called
710 principal components. PCA's parameter c refers to the number of principal
711 components to be used.

712

713 **Table S1: Predictive performance obtained using different smoothing filters**

Post-processing technique	Sensitivity	Specificity	AUC
Basic variables	80	78	82
Median Filter $s = 2$	79	77	81
Median Filter $s = 5$	77	76	80
Median Filter $s = 7$	75	75	79
Median Filter $s = 9$	73	74	77
Savitzky-Golay Filter $s = 3, d = 2$	80	78	82
Savitzky-Golay Filter $s = 5, d = 2$	79	78	82
Savitzky-Golay Filter $s = 5, d = 3$	79	78	82
Savitzky-Golay Filter $s = 7, d = 2$	78	78	82
Savitzky-Golay Filter $s = 7, d = 3$	78	78	82
Savitzky-Golay Filter $s = 9, d = 2$	78	77	82
Savitzky-Golay Filter $s = 9, d = 3$	78	77	82
Wiener Filter $s = 2$	79	78	82
Wiener Filter $s = 5$	78	78	82
Wiener Filter $s = 7$	78	78	82
Wiener Filter $s = 9$	78	78	82

714

715 AUC = area under the receiver operating characteristic curve.

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721 **Table S2: Predictive performance obtained using standardisation and normalisation +/-**
722 **smoothing filter**

Post-processing technique	Sensitivity	Specificity	AUC
Basic variables	80	78	82
Standardisation applied to basic variables	87	84	83
Standardisation applied to variables with Savitzky-Golay Filter $s = 3, d = 2$	87	84	83
Normalisation applied to basic variables	75	89	83
Normalisation applied to variables with Savitzky-Golay Filter $s = 3, d = 2$	75	89	83

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724 AUC = area under the receiver operating characteristic curve.

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736 **Table S3: Predictive performance obtained using difference and slope +/-**
 737 **standardisation +/- smoothing filter**

Post-processing technique	Sensitivity	Specificity	AUC
Basic variables	80	78	82
Difference $d = \{1,2,3,4,5\}$ applied to basic variables	84	84	72
Difference $d = \{1,2,3,4,5\}$ applied to variables with Savitzky-Golay Filter $s = 3, d = 2$	84	84	72
Difference $d = \{1,2,3,4,5\}$ applied to variables with Standardisation	84	84	72
Difference $d = \{1,2,3,4,5\}$ applied to variables with Savitzky-Golay Filter $s = 3, d = 2$ and Standardisation	84	84	72
Slope, $d = \{1,2,3,4,5\}$ applied to basic variables	91	72	54
Slope $d = \{1,2,3,4,5\}$ applied to variables with Savitzky-Golay Filter $s = 3, d = 2$	91	72	54
Slope $d = \{1,2,3,4,5\}$ applied to variables with Standardisation	92	68	54
Slope $d = \{1,2,3,4,5\}$ applied to variables with Savitzky-Golay Filter $s = 3, d = 2$ and Standardisation	92	68	54
Slope $d = \{1,2,3,4,5\}$ applied to variables with Savitzky-Golay Filter $s = 3, d = 2$, Standardisation and Difference $d = \{1,2,3,4,5\}$	92	75	63

738

739 AUC = area under the receiver operating characteristic curve.

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744 **Table S4: Comparison of machine learning model performance**

Machine learning model	Sensitivity	Specificity	AUC
Decision tree	8	100	52
Naïve Bayes	80	84	82
Perceptron	96	69	-
Logistic regression	86	86	84

745

746 AUC = area under the receiver operating characteristic curve.

747 These values have been obtained after a grid search to tune the parameter values below, based
 748 on one run of 5-fold stratified cross validation for each combination of parameter values. The
 749 values in bold obtained the best results.

750 • Decision tree:

751 ○ Split criterion {**gini index**, entropy}

752 ○ Split strategy {best, **random**}

753 • Naïve Bayesian:

754 ○ Prior probabilities of the classes {**none**, $(1 - 10^{-2}, 10^{-2})$, $(1 - 10^{-3}, 10^{-3})$, $(1 -$
 755 $10^{-4}, 10^{-4})$ }

756 • Perceptron:

757 ○ Regularisation method {11, **l2**}

758 ○ Tolerance for stopping criterion {**none**, 10^{-3} , 10^{-4} }

759 • Logistic regression:

760 ○ Regularisation method {11, **l2**}

761 ○ Tolerance for stopping criterion { 10^{-3} , **10^{-4}** }

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763

764 **Table S5: Comparison of class imbalance learning techniques**

Technique	Sensitivity	Specificity	AUC
No resampling	0	100	82
Under-sampling <i>r</i> =25%	55	97	83
Under-sampling <i>r</i> =50%	72	93	83
Under-sampling <i>r</i> =75%	81	89	83
Under-sampling <i>r</i> =100%	87	84	83
Over-sampling <i>r</i> =25%	55	97	83
Over-sampling <i>r</i> =50%	72	93	83
Over-sampling <i>r</i> =75%	81	89	83
Over-sampling <i>r</i> =100%	87	84	83
SMOTE <i>r</i> =25%	54	97	83
SMOTE <i>r</i> =50%	72	93	83
SMOTE <i>r</i> =75%	81	89	83
SMOTE <i>r</i> =100%	87	84	83

765

766 AUC = area under the receiver operating characteristic curve; SMOTE = synthetic minority
 767 over-sampling technique; *r* = ratio of exacerbation and non-exacerbation training examples
 768 obtained by resampling.

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775 **Table S6: Comparison of variable selection and data reduction techniques**

Post-processing technique	Sensitivity	Specificity	AUC
Recursive feature elimination	88	83	86
PCA $c = 3$	83	69	73
PCA $c = 5$	84	68	73
PCA $c = 9$	85	69	73
PCA $c = 20$	87	79	79
PCA $c = 40$	88	82	85
PCA $c = 60$	89	83	86
PCA $c = 80$	90	83	85
PCA $c = 100$	90	82	84

776

777 AUC = area under the receiver operating characteristic curve; PCA = principal components
 778 analysis.

779 c = number of components