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Stratifying asthma severity in children using cough sound analytic technology

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ABSTRACT

Introduction: Asthma is a common childhood respiratory disorder characterized by wheeze, cough and respiratory distress responsive to bronchodilator therapy. Asthma severity can be determined by subjective, manual scoring systems such as the Pulmonary Score. These systems require significant medical training and expertise to rate clinical findings such as wheeze characteristics, and work of breathing. In this study, we report the development of an objective method of assessing acute asthma severity based on the automated analysis of cough sounds.

Method: We collected a cough sound dataset from 224 children; 103 without acute asthma and 121 with acute asthma. Using this database coupled with clinical diagnoses and Pulmonary Scores (PS) determined

by a clinical panel, we developed a machine classifier algorithm to characterize the severity of airway constriction. The performance of our algorithm was then evaluated against the PS from a separate set of patients, independent of the training set.

Results: The cough-only model discriminated no/mild disease (PS 0-1) from severe disease (PS 5,6) but required a modified respiratory rate calculation to separate very severe disease (PS>6). Asymptomatic children (PS 0) were separated from moderate asthma (PS 2-4) by the cough-only model without the need for clinical inputs.

Conclusion: The pulmonary score provides information in managing childhood asthma but is not readily usable by non-medical personnel. Our method offers an objective measurement of asthma severity which does not rely on clinician-dependent inputs. It holds potential for use in clinical settings including improving the performance of existing asthma-rating scales and in community-management programs.

Trial registration: Australian and New Zealand Clinical Trial Registry- ACTRN12618001832268

KEYWORDS: ALGORITHM DEVELOPMENT, WHEEZE, PULMONARY SCORE, SOUND-ANALYSIS.

INTRODUCTION

Asthma is a common childhood disorder affecting 11% of Australians; it is the leading cause of non-fatal disease burden in Australians aged under 14 years [1, 2]. Acute asthma is characterized by episodic, reversible airflow obstruction and presents with wheeze, respiratory distress and cough responsive to bronchodilator medication [3]. The underlying pathophysiology is airway inflammation causing restricted airflow through partially constricted small and large airways, creating wheeze and increased work of breathing, manifesting as increased respiratory rate and accessory muscle use. Wheeze characteristics may change with increasing obstruction, while in severe disease there may be insufficient airflow to generate any wheeze, resulting in a “silent chest”.

The assessment of asthma severity is an essential component of management in clinical practice but can be difficult and is subject to interpretation. Asthma management protocols rely on caregivers to grade

acute asthma into severity categories even though clinical assessment is subject to poor inter-rater reliability [3, 4]. In wheeze severity assessments for children under six years, there was 52% agreement between nurses and pediatricians; and 32% agreement between parents and pediatricians [5]. In children under 18 months, studies have shown poor levels of agreement even amongst respiratory physicians using auscultation ($\kappa = 0.18$ (95% CI=-0.08-0.44)) [6]. The ability to detect wheeze by auscultation is dependent on (i) the sound being generated within the lungs with sufficient intensity to reach the chest wall to be detected by a stethoscope; (ii) the clinician having sufficient hearing acuity; and (iii) clinical skill and experience to recognize its defining characteristics.

Various measures of airway obstruction have been developed. Objective tests include spirometry and Peak Expiratory Flow Rate (PEFR) measurements [7]. In acute settings, formal spirometry is not available or practical and is unreliable in children under seven years. The PEFR meter has the advantage of being inexpensive and portable. However, young children (<6 years) and those in significant respiratory distress are often unable to comply with PEFR tests. PEFR measurement is not recommended for routine use in children under 12 years [3].

Clinical rating scales use combinations of clinical features to guide asthma management, gauge response to therapy, and to determine the urgency of care. The Pulmonary Score (PS) is an asthma severity scale commonly used in clinical practice and is comparable to PEFR [4]. It is regularly used in Western Australian hospitals and is relied on in routine clinical practice [8]. The PS utilizes respiratory rate (RR), wheeze characteristics and accessory (sternocleidomastoid) muscle (AM) use to generate a score out of 9 (Table 1). Respiratory rates can readily be determined. The assessment and grading of wheeze characteristics and AM use, however, require significant training and expertise. While the PS can provide critical information in managing childhood asthma in all settings, it is not a practical assessment tool outside of clinical practices or hospitals. The primary aim of this study was to identify meaningful groups of asthma severity as characterized by the PS using simple community-deployable technology that does not require expert input.

In previous work, we have shown that cough analysis can predict spirometry results in adults [9]. We have developed similar techniques to accurately identify common childhood respiratory disorders (asthma, pneumonia, bronchiolitis, croup, lower respiratory tract disease) from a cohort of mixed undifferentiated respiratory conditions [10-13]. For Asthma detection, we achieved a 97% positive percent agreement and 91% negative percent agreement with a consensus panel of pediatricians [14].

During a cough, the lungs are directly connected to the atmosphere creating a high bandwidth channel through which lung sound components can propagate outside the body [10]. Cough sounds embed acoustic signatures such as the resonating airways or shape changes in the cough signal envelope such as a slower decaying tail-end due to constrictions (Figure 1). We propose that asthma severity can be characterized using the mathematical analysis of spontaneous or voluntary cough sounds by extracting and mapping sound signatures in different PS categories. The method is not limited to identifying the existence of conventional wheeze.

Using a clinical database of cough sounds coupled with clinical diagnoses and PS values determined by a specialist clinician panel, we developed a machine learning algorithm to map cough features into PS severity bands.

METHODS

Study Design:

This was a prospective observational study. Ethical approval was obtained from the Human Research Ethics Committees at The University of Queensland, Joondalup Health Campus and Princess Margaret Hospital. Informed consent was obtained.

Study population:

Between March 2015 and December 2016, a convenience sample of children aged 29 days to 12 years was recruited into the “Breathe Easy” study (ACTRN12618001521213) at two hospitals; Joondalup

Health Campus (JHC) and Princess Margaret Hospital (PMH), Perth, Western Australia. Over 100,000 children attend the Emergency Departments of these hospitals annually. Enrollment occurred in multiple locations, including ambulatory care units, inpatient wards and Emergency Departments (ED). Inclusion - and exclusion criteria are shown in Table 2.

From this cohort, we identified children with a diagnosis of acute asthma for this study. Also, we recruited asymptomatic participants (both with and without a history of asthma) with no clinically discernible respiratory signs. All subjects had the same rigorous medical screening and examination processes.

Study protocol:

The study did not interfere with the clinical care; thus any treatment given to the child (including bronchodilators) was at the discretion of the treating team. The cough recordings, clinical examination and PS calculation were performed at the same time by specialist pediatric nurses.

Clinical Case Definitions:

a) Acute Asthma: A respiratory event in a child with wheeze, or a silent chest during auscultation, responsive to a Bronchodilator Test (BT). A BT consisted of the administration of Salbutamol MDI via spacer up to 3 times over one hour at the following doses: 6 puffs for children < 6 yrs, 12 puffs for children > 6 yrs. Bronchodilator responsiveness was confirmed by the treating medical team.

b) Asymptomatic individuals: Children with no acute respiratory symptoms or clinically discernible respiratory signs. By definition, all subjects in the asymptomatic group had a PS score of 0. This group consisted of subjects with:

- i) no previous history of asthma;
- ii) a history of asthma using prophylactic medication;
- iii) a history of asthma not using prophylactic medicine.

The clinical panel confirmed acute asthma diagnosis after review of all clinical records, including BT responsiveness and investigations. Parents/caregivers reported asthma history and current preventer medication use.

Cough Recording:

The recording device was an iPhone 6 (Apple, California, USA) held 25-50cm away from the mouth with the microphone angled towards the subject at 45 degrees [12]. Sound data were recorded at a sampling rate of $f_s = 44.1$ kHz with a 16-bit resolution. A pediatric research nurse undertook recordings in realistic hospital environments where background noises included talking, crying, medical devices, footsteps and doors. Care was taken not to record coughs from other people or in the presence of preventable interferences such as television sounds or loud conversations. Each cough recording took less than five minutes.

A minimum of five spontaneous or voluntary coughs were recorded from each child. Asymptomatic subjects could only provide voluntary coughs.

Calculation of PS Scores:

We calculated PS scores at the same time as the cough recording and clinical examination according to the criteria shown in Table 1. Specialist pediatric nurses experienced in using the PS system assessed AM use and wheeze characteristics.

The Clinical Dataset:

We divided the dataset into the following groups (Table 3):

- i Acute Asthma ($\mathcal{Y}$): Let $\mathcal{Y}_{i-j}$ represent the set of contiguous PS values given by $\mathcal{Y}_{i-j} = \{PS=i, i+1, \dots, j\}$. In this work we considered three different subgroups symbolized by $\mathcal{Y}_{5-9}$, $\mathcal{Y}_{2-4}$ and $\mathcal{Y}_{0-1}$. The first subgroup (PS 5-9) $\mathcal{Y}_{5-9}$ which included subjects with PS = {5,6,7,8,9} represented severe airway restriction; the 2nd subgroup (PS 2-4) $\mathcal{Y}_{2-4}$ represented

moderate restriction with $PS = \{2,3,4\}$ and the 3rd subgroup $\mathcal{Y}_{0,1}$ (PS 0-1) symbolized minor (or insignificant) restriction with $PS = \{0,1\}$. These three subgroups were separated as such to represent distinct clinical scenarios, each requiring different management [8].

ii Asymptomatic (N): We divided subjects with no active disease ($PS=0$) into three subgroups: $N_{NH}=\{\text{those without a history of viral wheeze/asthma}\}$, $N_{AH}^{NP}=\{\text{those with a history of viral wheeze/asthma but not taking any preventer medications at the time of recruitment}\}$, and $N_{AH}^P=\{\text{those with a history of viral wheeze/asthma and taking preventer medications at the time of recruitment}\}$ to ascertain whether different histories or medication use affected the outcome. These three groups are considered identical (i.e., asymptomatic, $PS=0$) when assessed for the presence of acute asthma in a clinical setting.

Training Set (G1): Cough-based PS classifier Design and Cross-Validation separating PS 0-1 (no, mild) from $PS \geq 5$ (severe asthma):

Due to its dependence on subjective and difficult measurements, the PS, as estimated by the clinical process, can only be considered a gross measure. Taking this into account we initially trained a Logistic Regression (LR) classifier with the target of separating the subjects in $\mathcal{Y}_{5-9}$ from that of the combined group $\{\mathcal{Y}_{0,1} + N_{AH}^P\}$. The group defined by $G1=\{\mathcal{Y}_{0,1} + N_{AH}^P + \mathcal{Y}_{5-9}\}$ ($n=60$) is the model training and validation set comparing PS 0-1 to $PS \geq 5$. We used a leave-one-out cross-validation method [10] to develop and validate the models, which involves using data from all the patients in G1 except one to train the model and cough events from the remaining patient to validate the model. Candidate features were computed from the whole of G1. This process was systematically repeated such that each patient in G1 is used once as the validation subject. LR is a linear model, which uses several independent features to estimate the probability of a categorical event (dependent variable). We set the dependent variable $Y=1$ when we have a subject in G1 belonging to $\mathcal{Y}_{5-9}$, and set $Y=0$ otherwise. A model is

derived using a regression function to estimate the probability of Y given the independent input features (i.e., $\mathbf{F}_{ca} = \{f_{0c}, f_1, f_2, \dots, f_f\}$) as:

$$Prob(Y) = \frac{e^z}{e^z + 1} \quad (1)$$

$$z = \beta_0 + \beta_1 \cdot f_{0c} + \beta_2 f_2 + \beta_{n-1} f_F \quad (2)$$

The function in (1) gives a continuous output of probabilities. A decision threshold to determine if a given subject belongs to $\{Y_{5-9}\}$ or $\{Y_{0,1} + N_{AH}^P\}$ was computed using the Receiver Operating Curve (ROC).

The method of extracting the input cough features is summarised below:

- (i) Let $\mathbf{x}$ denote a discrete time sound signal from an arbitrary cough event.
- (ii) Segment $\mathbf{x}$ into three equal-sized non-overlapping sub-segments. Let $\mathbf{x}_i$ represents the i^{th} sub-segment of $\mathbf{x}$, where $i = 1, 2, 3$. From each sub-segments $\mathbf{x}_i$ compute the following features [10]: Bispectrum Score (BGS), Non-Gaussianity score (NGS), the first four formant frequencies (FF), log energy (LogE), zero crossing (ZCR), kurtosis (Kurt), and twelve Mel-frequency cepstral coefficients (MFCC).
- (iii) Using the whole cough event $\mathbf{x}$, compute 13 wavelet features based on the Morlet wavelet as detailed previously [11].

A total of 76 features were extracted from each cough event to form a feature vector $\mathbf{F}_c$.

We trained LR models using several different approaches. In the purest form, we used only cough features for LR training. To investigate the relative importance of the individual clinical sub-components on the overall clinical PS (Table 1), we also developed LR models using RR and AM as individual inputs. Finally, we augmented cough features with information derived from the respiratory rate, on the basis that such information will be readily reportable by patients or guardians even in a home setting. On the contrary, AM and wheeze severity estimation require clinical respiratory expertise and are not

reportable by laypersons. Since our target is to develop a community deployable technology, we saw no purpose in using AM or wheeze severity to augment cough features.

In our LR models, we transformed the RR into another feature, the *Breathing Index (BI)* defined as the difference between the measured respiratory rate and the age-specific thresholds of 40 breaths per minute for children aged under 60 months and 20 breaths per minute for children aged over 60 months [10]. Normative RRs for younger children are known to be higher than those of older children, and the BI attempts to codify that [15, 16]. In our models, the AM use was graded as per the PS scoring system into none, mild increase, increased and maximal activity (table1).

Independent testing set (G2) using the generated model to separate PS 0 (no disease) from PS 2-4 (moderate asthma):

Once the LR model training was finished following the cross-validation process, we selected one model following the philosophy in [10]. We fixed the parameters of this model and undertook a performance analysis by testing it on a hitherto unused test set: $G2 = \{Y_{2-4} + N_{AH}^{NP} + N_{NH}\}$ (n=164) representing subjects with moderate disease and those with no clinically discernible disease. Note that sets G1 and G2 are mutually exclusive and that the two groups use separate sets of PS 0-1.

Results

Study population:

Two hundred twenty-four subjects were included for analysis, of which 103 had no acute respiratory disease, and 121 had acute asthma. Table 3 describes the subject demographics, cough characteristics and separation into training and independent groups. No subjects with PS > 7 were enrolled as they met the exclusion criteria of medical instability. We analyzed a total of 3161 cough episodes.

The ages of subjects in the asymptomatic group were significantly older than the asthmatic group as a whole ($p < 0.0001$). There was no age difference between asthmatic subjects with $PS=0,1$ and $PS\ 2-4$ ($p=0.45$) nor between the groups $PS=2-4$ and $PS \geq 5$ ($p=0.15$).

Training Set (G1): Cough-based PS classifier Design and Cross-Validation separating PS 0-1 (no, mild) from $PS \geq 5$ (severe asthma):

The LR model based on cough features alone was able to separate groups $PS \geq 5$ from $PS \leq 1$ with a sensitivity of 82.61% and specificity of 78.38% (Table 4). The results show that cough sounds carry information for the separation of these PS groups.

As expected by their being components of the clinical pulmonary score, BI and AM-use also independently separated groups $PS \geq 5$ and $PS \leq 1$. BI alone achieved similar results to cough analysis alone (sensitivity 69%, specificity 81%). The addition of cough features to BI improved sensitivity to 91% and specificity to 97%. AM use on its own achieved sensitivity of 100% and specificity of 94%, which was not enhanced by the addition of the cough model. Since AM use is rarely seen in mild asthma but is always present in severe asthma, it is not surprising that this component of the PS performed well in this context.

Addition of BI to cough-alone model allowed separation of the very severe cases ($PS=7$) from no/mild disease ($PS\ 0,1$) (Figure 2).

Independent testing set (G2) using the generated model to separate PS 0 (no disease) from PS 2-4 (moderate asthma):

To investigate the performance of the LR models in separating $PS\ 0$ from $PS\ 2-4$ (moderate disease), we picked one LR model and tested it on the independent test set $G2\ \{\mathbf{Y}_{2-4} + \mathbf{N}_{AH}^{NP} + \mathbf{N}_{NH}\}$. The aim was to examine whether the continuous output of the trained LR function in (1) showed any relationship to PS values for moderate disease. Two different groups of asymptomatic subjects ($PS=0$) were pooled for this

analysis (N_{NH} and N_{AH}^{NP}), neither of which had been used in the G1 test set. Comparing this pooled group against the asymptomatic group tested in G1 evaluates the discriminatory ability of the algorithm to detect subclinical respiratory conditions.

Figure 2 shows the LR output from each model tested (means and 95% CI) based on all recorded cough events ($n=3161$). Though the LR models were trained to separate the subjects with $PS \geq 5$ from subjects with $PS \leq 1$, testing in a second cohort also demonstrated the separation of PS 2-4 and asymptomatic subjects, N_{NH} and N_{AH}^{NP} .

Cough alone, but not BI alone, discriminated between PS 0 and PS 2-4. AM use alone was the best single clinical parameter in separating the PS <4; however, did not differentiate above this level (Fig. 2).

The two asymptomatic groups ($PS=0$: G1 and G2) differed significantly in age (mean difference 22 months, SE 7, $p<0.0022$) however the mean LR outputs did not differ between groups for the cough only ($p=0.5$), BI only ($p=0.7$) or combined cough and BI models ($p=0.4$) (Fig. 2).

DISCUSSION

Grading acute asthma severity is an integral component of disease management. Clinical care protocols rely on severity assessments and scoring systems such as the PS are used to help with clinical decisions such as treatment initiation and response, level of clinical monitoring, and discharge planning. However, many scales have not been adequately evaluated and rely on the subjective evaluation of signs such as wheeze characteristics and inspiratory/expiratory wheeze ratios. A systematic review of 64 studies concluded that none of the tested pediatric asthma scores had been appropriately validated [17]. Similar conclusions have been found in preschool-aged children [18]. The PS is the most extensively used assessment tool in Western Australian pediatric emergency departments and rapidly codifies acute asthma symptoms to a severity score which is used to guide treatment according to established protocols [8]. The intent of this study was to replicate the discriminatory ability of the PS using a tool that does not require the input of experienced health professionals.

Our results from 224 patients are encouraging and demonstrate that cough carries useful information on asthma severity. We have developed a cough-only model that is an accurate reflection of PS in children with no (PS 0), mild (PS 1) and moderate asthma (PS 2-4). The cough-only model performance degraded above PS 5 and required a single simplified component (respiratory rate) of the original PS to correct. Adding RR (as BI) to the algorithm provided further separation of very severe (PS 7) from no/mild asthma (PS 0,1). In severe asthma, airway obstruction can increase to a point where little air can pass through the airways and auscultation may fail to detect wheeze. This is accounted for in the original PS where those without wheeze due to minimal air exchange are given a maximum score. Similar to our cough analytic method, the PS scale has been reported to correlate better with lesser degrees of airway obstruction [4]. The algorithm is thus trained to recognize that the combination of a silent chest (altered acoustic signature) and a significantly elevated RR indicates increased levels of airway obstruction. The PS and algorithm both take into consideration the age-dependent variability in RR when determining the degree of disease severity.

A clinically important scenario is to separate no (PS 0) from moderate disease (PS 2-4) which we have demonstrated in our independent testing set (Figure 2, right panel). Although mild (PS 1) cases were not included in the testing set (G2), based on data from the training set (G1), we expect the probability output for PS 1 to be similar to PS 0 and distinct from the moderate disease group (PS 2-4). Importantly, under current care protocols, PS 1 patients would be managed in the same manner as PS 0 patients and differently to moderate cases (PS 2-4) for whom salbutamol is administered more frequently and steroids may be considered [8]. The discriminatory ability of the algorithm to separate cases of no disease (PS 0) vs. moderate disease (PS 2-4), is bolstered by the fact that the data used in the second test is hitherto untested data.

In practical terms, the discrimination of moderate from mild or absent disease can be difficult for the inexperienced practitioner or non-professional. The determination of increased RR and AM use

identifies severe exacerbations accurately, but these signs are less definitive in diagnosing the presence of mild disease. Mild exacerbations may present with a minimal increase in RR and an absence of AM use, leaving wheeze assessment, a technique which requires considerable expertise, as the sole basis for therapeutic decision making. Also, the identification and grading of AM use requires clinical training and is not usable by parents, caregivers or inexperienced clinicians. In contrast, our model requires no input of additional clinical signs for moderate disease (below PS of 5) and only a simple RR count above this level.

Two groups of asymptomatic children were compared (PS=0). We wished to ascertain whether there were discernible differences in algorithm detection performance amongst asymptomatic individuals. The first group consisted of children with chronic asthma controlled on preventers, while the second contained a group of children who had previously wheezed or who had never wheezed. No difference in the LR output between the groups was identified, suggesting a lack of effect from subclinical airway disease in our population.

There were several limitations to the study. Due to the experimental design, we have not been able to examine the differences between moderate and severe disease. There were fewer subjects with severe asthma (PS>5) compared to mild and moderate disease.

There are inherent problems in using the PS as a reference classifier due to subjectivity, poor validity, inter-rater reliability and reproducibility. For this reason, we elected to train the algorithm using the highest and lowest severity data and then the developed model was tested on lower acuity cases (PS<5). Due to the small numbers of subjects in these groups, it would be beneficial to undertake more extensive studies and also to evaluate the algorithm against objective measures of airway obstruction, including FEV1 and PEFr where practical.

There were age differences in subjects with and without active disease but not between subjects with mild and moderate or moderate to severe acute asthma. The control group subjects were generally older than those with acute asthma due to difficulties in obtaining voluntary coughs from asymptomatic children

under two years. However, children of any age with acute asthma exacerbations tend to cough spontaneously. The two groups of PS=0 (G1 and G2) differed significantly in age however it is interesting that the LR outputs did not differ, suggesting that age may not be an important variable in children without acute asthma. Accurately detecting the absence of acute asthma is important in clinical care and the decision of whether to commence appropriate treatment.

The PS and other similar systems are routinely used in younger children despite only being validated in older groups due to difficulty in obtaining accurate lung function parameters. Our system can be used at any age if the child is spontaneously coughing and from 2-3 years of age if voluntary coughs are required. This allows use in children below the lower age limit of 6-7yrs for spirometry or peak flow measurements.

The cough analyzer technology can be integrated onto a smartphone. This offers advantages including accessibility, portability, and ease of use, making it suitable for home monitoring and integration with asthma management plans. Asthma management plans require caregivers to assess severity promptly. Measuring respiratory rate is easier for caregivers than assessing the degree of accessory muscle use or the extent of wheeze (Table 1). Our model may improve the initiation and compliance with Asthma Action Plans as it only requires cough and RR assessment.

There is potential for use in telehealth consultations during which there is no opportunity for clinicians to perform an examination. Respiratory illnesses account for more than 30% of telehealth consultations [19]. The measurement of RR could be easily added to a cough-based model as it is objective and readily calculated during a video-conference. It may also be of value in remote area medicine where access to trained clinical personnel is limited. In such areas, the routine of measuring respiratory rates is well established in the hands of community healthcare workers using the WHO algorithm for detecting childhood pneumonia [20].

Future studies with larger numbers are required for prospective clinical testing. Separating the severity groups more fully would be advantageous. These studies should also look at the ability of the technology to monitor asthma response pre- and post-bronchodilator therapy and examine results in comparison to other commonly used asthma scoring systems or PEFr measurements in appropriately aged children. Longitudinal studies in subjects with asthma would help to define its role in the monitoring and management of chronic asthma.

CONCLUSION

We have demonstrated that cough carries significant information on asthma severity. Automated cough analysis alone separated no disease from moderate disease, with the addition of a simple RR method enabling further separation of no/mild disease from severe disease when compared to a common asthma severity scale (PS). The technology may have a place in hospitals to assist with initial treatment, admission and monitoring decisions and in the community in the use of asthma action plans. The method is objective and accessible to caregivers of diverse expertise.

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DECLARATIONS

Ethics approval and consent to participate

Ethical approval was obtained from the Human Research Ethics Committees of Princess Margaret Hospital (2015030EP), Joondalup Health Campus (1501), Curtin University (HRE2018-0016) and The University of Queensland (2015000395 / 2016.01.179). All participants, parents, or guardians signed a consent to participate form.

Code, Data and Materials Availability

The underlying codes are the property of ResApp Health and are not available. The cough recordings are not available but will be uploaded as an educational tool in the future.

Competing interests

UA and PP are scientific advisors and shareholders in ResApp Health (RAP). UA held the Chief Scientist/consultant positions at ResApp (June 2017-May 2019). RAP is commercializing the technology under license from the University of Queensland, where UA is employed. UA and VS are named inventors of related UQ technology. JT, TW, JC and VS are shareholders in RAP. UA currently holds a consultancy at RAP through UQ. JB declares no conflict.

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Author contributions

VS and UA designed the study and conducted mathematical work. PP and UA designed the Breathe Easy study. PP coordinated the clinical and recording data collection. UA led the algorithm development team. VS, UA and PP produced the first draft with all authors adding and revising the manuscript.

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LIST OF ABBREVIATIONS

AM: Accessory Muscle

BI: Breathing Index

CI: Confidence interval

FEV1: Forced expiratory volume in one second

LR: Logistic regression

PEFR: Peak expiratory flow rate

PS Pulmonary Score

RR: Respiratory Rate

SD: Standard deviation

SE: Standard Error

WA: Western Australia

Table 1: The Pulmonary Score. Clinicians estimate sub-scores (0-3) from the respiratory rate, wheeze and the accessory muscle use. The overall PS is the sum of all three sub-scores.

		Score (total out of 9)			
		0	1	2	3
Respiratory rate (RR)	<6yrs	<30	31 – 45	46 – 60	>60
	≥6yrs	<20	21 – 35	36 – 50	>50
Wheezing		None	End expiratory with stethoscope	Entire expiration with stethoscope	Inspiration and expiration without stethoscope (or no wheezing due to minimal air exchange)
Accessory muscle use (AM)		None	Mild increase	Increased	Maximal activity

Table 2: Breathe Easy Study inclusion and exclusion criteria

CLINICAL INCLUSION CRITERIA
At least one of the following: • Rhinorrhoea • Cough • Wheeze • Stridor • Increased work of breathing • Shortness of breath
CLINICAL EXCLUSION CRITERIA

- Lack of consent
- No respiratory disease
- Mechanical ventilation (invasive, CPAP, or BiPAP) or high-flow nasal cannula
- Unable to provide at least five coughs (voluntary or spontaneous)
- Medical contraindication to voluntary cough, including
 - Severe respiratory distress
 - History of pneumothorax
 - Eye, chest, or abdominal surgery past three months
- Too medically unstable to participate in the study as per treating clinician
- Structural airway disease including laryngo/tracheomalacia.

Table 3: Subject Demographics and Cough Characteristics:

Patient Subgroup	n	Age (months±SD)	Male: Female	Total Coughs
<i>Asymptomatic (no active disease)</i>	103	100.5±28.0	64:39	1244
N_{NH}^b	64	103.31±29.00	40:24	781
$N_{AH}^{NP\ b}$	19	113.95±31.69	9:10	259
$N_{AH}^P\ ^a$	20	80.70±22.01	15:5	204
<i>Acute Asthma</i>	121	62.3 ±29.9	79:42	1917
$\gamma_{0,1}\ ^a$	17	69.06±21.07	14:3	276
$\gamma_{2-4}\ ^b$	81	63.61±31.25	50:31	1285
$\gamma_{5-9}\ ^a$	23	52.83±32.14	15:8	356

* $G1$ (training and validation set), ^{b} $G2$ (independent testing set)

Table 4: Training set (G1) – Leave-one-out validation results for separating subjects with $PS \geq 5$ from the subjects with $PS \leq 1$.

Diagnostic features	Sensitivity %	Specificity %	Accuracy %
Cough	82.61	78.38	80.00
Breathing Index	69.57	81.08	76.67
Accessory muscle use	100.00	94.59	96.67
Breathing Index +cough	91.30	97.30	95.00

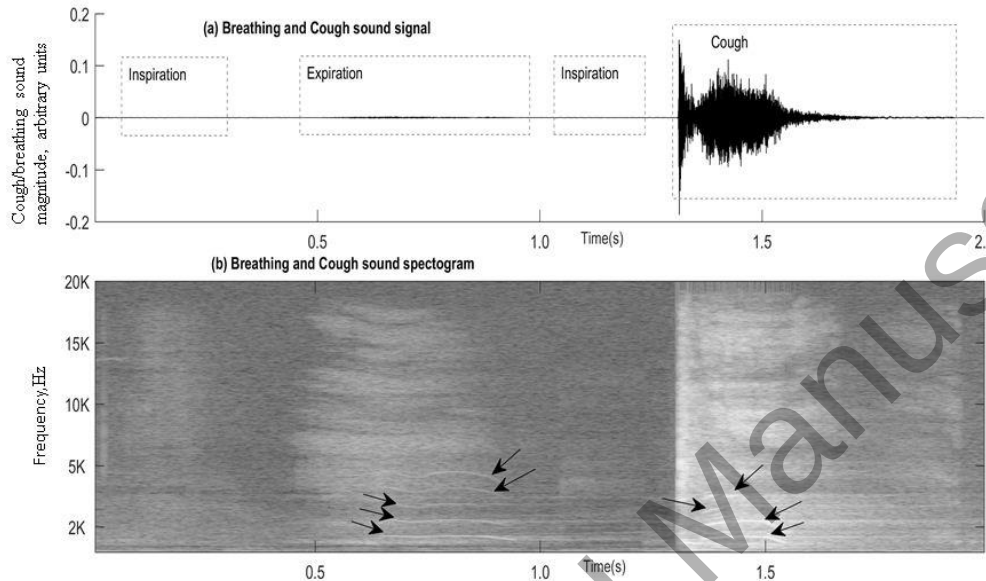


Figure 1: (a) An example breathing and cough sound signal obtained from a patient with wheeze and (b) their spectrogram. Spectrogram of the cough signal shows that conventional wheezing (horizontal lines as indicated using arrows) in breathing may be seen within a cough. Wheezing is an externally observable sign associated with the underlying phenomenon of constricted airways. It is caused by resonance in constricted airways during air movements.

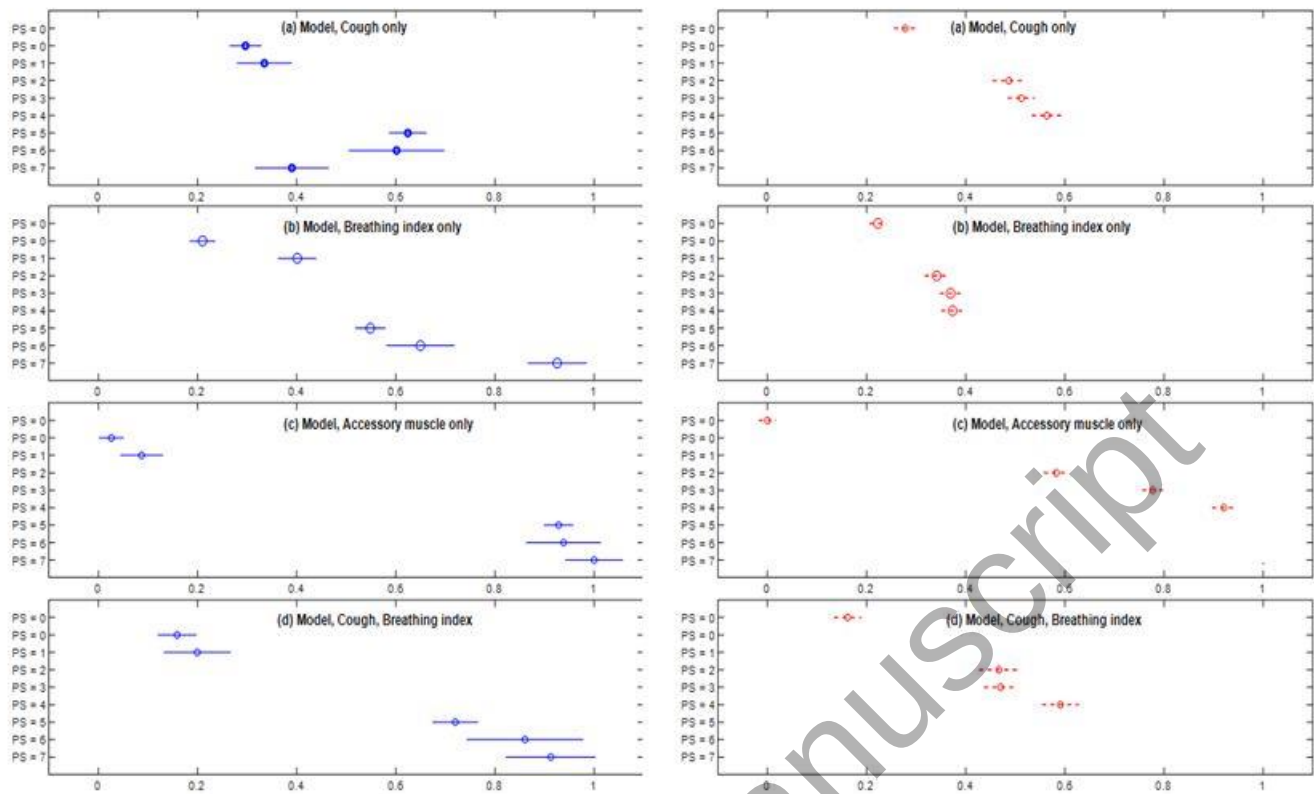


Figure 2. Mean logistic regression output (continuous probability) with 95% confidence intervals (horizontal bars) for different PS scores (all cough events) — Training Set (G1): Cough-based PS classifier separating PS 0-1 (no/mild asthma) from PS ≥ 5 (severe asthma) ----- Independent testing set (G2): Using the generated model to separate PS 0 (no asthma) from PS 2-4 (moderate asthma). The number of data points at the PS values 0(G1), 0(G2), 1, 2, 3, 4, 5, 6, 7, 8, 9 are 333, 1040, 147, 387, 476, 422, 233, 54, 69, 0, 0. (n=3161)