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Comorbidities in Difficult Asthma are Independent Risk Factors for Frequent Exacerbations, Poor Control, and Diminished Quality of Life

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Summary at a glance

This study examined comorbidities in a consecutive cohort of difficult asthma patients.

Increasing body mass index, chronic rhinosinusitis, dysfunctional breathing and vocal cord

dysfunction were independent risk factors for a broad spectrum of asthma outcomes.

Identification and treatment of these comorbidities are essential in management of patients with difficult asthma.

Abbreviations

ACT = Asthma Control Test, Anx/Dep = Anxiety or depression, AQLQ = Asthma Quality of Life Questionnaire, AR = Allergic rhinitis, BMI = Body mass index, CRS = Chronic rhinosinusitis, DB = Dysfunctional breathing, GORD = Gastroesophageal reflux disease, OSA = Obstructive sleep apnoea

ABSTRACT

Background and objective

Little is known about how comorbidities affect difficult asthma patients across different domains of asthma outcomes. We hypothesised that comorbidities in difficult asthma significantly influence asthma outcomes.

Methods

We analysed 90 consecutive patients who underwent systematic assessment at our hospital's difficult asthma clinic. Eight comorbidities were assessed in all patients. They were allergic rhinitis (AR), chronic rhinosinusitis (CRS), gastroesophageal reflux disease (GORD), obesity, obstructive sleep apnoea (OSA), anxiety or depression (Anx/dep), dysfunctional breathing (DB) and vocal cord dysfunction (VCD). Asthma outcomes examined were exacerbation frequency (≥3 vs <3/year), asthma control using the Asthma Control Test (ACT), and quality of life using the Asthma Quality of Life Questionnaire (AQLQ). Multivariate logistic regression was performed for dichotomous outcomes and linear regression for continuous outcomes. Analyses were adjusted for lung function and absolute blood eosinophils.

Results

Increasing body mass index was an independent risk factor for exacerbations (OR 1.1: 95% CI 1-1.1, $p=0.042$), lower ACT score (B coefficient -0.25: 95% CI -0.37 to -0.12, $p<0.001$) and poorer AQLQ (B coefficient -0.05: 95% CI -0.09 to -0.02, $p=0.006$). DB predicted lower

ACT (B coefficient -2.85: 95% CI -5 to -0.7, $p=0.01$) and AQLQ scores (B coefficient -0.73: 95% CI -1.34 to -0.12, $p=0.02$). Patients with CRS had more exacerbations (OR 4: 95% CI 1.5-10.9, $p=0.006$). Patients with VCD had lower AQLQ scores (B coefficient -0.78: 95% CI -1.38 to -0.18, $p=0.012$).

Conclusion

Comorbidities independently impact a broad spectrum of outcomes in difficult asthma.

Systematic evaluation of these conditions is essential in difficult asthma.

Keywords

Asthma, body mass index, comorbidity, sinusitis, vocal cord dysfunction

Short title

Comorbidities in difficult asthma

INTRODUCTION

It is estimated that up to 17% of asthma patients have difficult asthma¹. These patients have poor asthma control or frequent exacerbations despite high-intensity asthma medication.^{1, 2}

This group of patients is heterogeneous. Some have truly treatment refractory asthma, while others may be difficult to treat due to other factors such as the presence of comorbidities.^{3, 4}

Comorbidities are common in patients with difficult asthma and they collectively affect more than half of this patient group.^{2, 5} The need for systematic evaluation of comorbidities has been heavily emphasised in asthma guidelines^{3, 6}, and proposed as an essential component of difficult asthma assessment.⁷

Traditional asthma parameters such as lung function and inflammatory biomarkers clearly affect asthma outcomes.^{8, 9} For example, sputum and blood eosinophilia is linked to more frequent asthma exacerbations.^{9, 10} There is increasing evidence that the presence of comorbidities also influences asthma outcomes.¹¹ However, most of these studies were conducted in the general asthma population.^{12, 13} Some studies have examined comorbidities in difficult asthma cohorts, but have not examined their effect across different asthma outcomes.¹⁴

To our knowledge, an analysis of how comorbidities in difficult asthma impact a broad spectrum of asthma outcomes has not been previously reported. We hypothesised that comorbidities would significantly influence important asthma outcomes in difficult asthma patients. We tested our hypothesis in a consecutive series of patients with difficult asthma, by systematically identifying comorbidities and assessing their impact on exacerbation frequency, symptom control, and asthma quality of life.

METHODS

Subjects

This cross-sectional analysis was performed on consecutive patients seen in our difficult asthma service from 1 June 2014 to 31 October 2015. Patients were referred from respiratory specialists throughout the state of Victoria, Australia. Patients were considered to have difficult asthma if the referring specialist experienced difficulty in managing the patient, and felt one or more of the following to be present: diagnostic dilemma, poor symptom control, frequent or severe exacerbations, poor lung function, or the presence of patient factors complicating management. This study was approved by the Alfred Health Ethics Committee (Reference number 285/15) and requirement for informed consent was waived.

Assessment

All patients underwent protocolised evaluation. Asthma history was obtained using a standardised electronic template. Pre and post-bronchodilator spirometry were performed for

all patients. The diagnosis of asthma was made based on consistent history with evidence of variable airflow obstruction (VAO). Presence of VAO was based on bronchodilator response, peak flow variability or bronchial provocation testing. If VAO was not demonstrable, asthma was diagnosed if the managing physician still felt asthma was the most likely diagnosis, after considering the clinical history and relevant investigations. Atopic status was assessed using skin prick tests and/or specific serum Immunoglobulin E (IgE) to a panel of common aeroallergens. The eosinophilic phenotype was determined based on blood eosinophils and exhaled nitric oxide (FENO).

Comorbidities

Eight comorbidities were specifically evaluated in all patients. They were: allergic rhinitis (AR), chronic rhinosinusitis (CRS), dysfunctional breathing (DB), vocal cord dysfunction (VCD), obesity, obstructive sleep apnoea (OSA), gastroesophageal reflux (GORD), and anxiety and depression (Anx/dep). Our clinic utilised validated screening questionnaires in addition to clinical assessment to aid the diagnosis of comorbidities (Supplementary Appendix S1). The diagnosis of each comorbidity was based on the criteria listed in Supplementary Appendix S2.^{15, 16, 17, 18, 19}

Asthma outcomes

Three asthma outcomes were examined: frequency of asthma exacerbations, asthma symptom control and asthma quality of life. Asthma exacerbations were defined by the requirement for systemic corticosteroid, or the need to increase the dose of systemic corticosteroid in those on maintenance therapy, for 3 days or more.²⁰ Patients were considered to have frequent

exacerbations if they reported 3 or more exacerbations in the 12 months preceding evaluation. The cut-off of 3 exacerbations per year allowed for comparison with an earlier study performed in the Netherlands which also examined risk factors for frequent exacerbations in a difficult asthma cohort.¹⁴ Asthma control was measured using the Asthma Control Test.²¹ The ACT score ranges from 5 to 25, with a higher score reflecting better asthma control. A score less than 20 indicates poor control. A change in ACT score of 3 represents a clinically meaningful change.²² Asthma quality of life was measured using the Asthma Quality of Life Questionnaire (AQLQ).²³ A lower AQLQ represents greater impairment of health status. A change in AQLQ total score of 0.5 from baseline represents a clinically meaningful change.²⁴

Statistical analysis

Gender, age, duration of asthma, absolute blood eosinophil count, pre-bronchodilator FEV₁ (%), smoking status and the 8 comorbidities were analysed as predictors in risk factor analyses for exacerbations, symptom control and asthma quality of life.

The number of asthma exacerbations was expressed as a dichotomous outcome (≥3 vs <3 per year). Predictors for asthma exacerbations were compared using unpaired t-test and chi square test where appropriate. Variables with p value <0.1 were then selected for inclusion in a multivariate logistic regression model.

ACT and AQLQ scores were expressed as continuous outcomes. Variables were analysed using linear regression. Variables with p value <0.1 were selected for inclusion in multivariate linear regression models.

A decision was made *a priori* to include blood eosinophils and pre-bronchodilator FEV₁ (%) in the multivariate logistic and linear regression models regardless of p values on univariate analyses, as these parameters have been shown to influence asthma exacerbations and asthma control^{8,9}.

Data was analysed using SPSS version 22 (IBM, NY). Continuous variables were expressed in mean (SD) and categorical variables are expressed as number (percentages).

RESULTS

Ninety consecutive patients were evaluated in our difficult asthma service. Their baseline characteristics are described in Table 1. Of the 90 patients, 39 (43.3%) had experienced 3 or more exacerbations in the preceding 12 months. The mean ACT score was 14 ± 5 and the mean AQLQ was 4.26 ± 1.45 . Comorbidities were common in our cohort, with 74.4% having 2 or more comorbidities. The prevalence of each comorbidity is presented in Table 1. All but 3 patients had maximisation of asthma medication to GINA step 4 or 5, or highest intensity tolerable. Three patients did not have escalation of asthma medication as symptoms improved with comorbidity management.

Following systematic assessment, 5 patients were thought not to have asthma. One patient had diagnosis of chronic obstructive pulmonary disease (COPD) based on his extensive smoking history and evidence of widespread emphysema on chest imaging. Two patients were diagnosed with VCD, one patient had dysfunctional breathing, and the last patient had both VCD and dysfunctional breathing. Asthma was excluded in these patients in view of the absence of VAO despite tapering asthma medications, and improvement of symptoms with speech and breathing retraining. Of the remaining 85 patients with asthma, all had evidence of VAO except for 9 patients. Asthma was thought to be the most likely diagnosis in these 9 patients by the managing physicians based on consistent clinical history and exclusion of other differential diagnoses.

Asthma exacerbations

On univariate analysis, patients with frequent exacerbations were more likely to be female and younger. They were also more likely to have CRS and VCD (Table 2).

On multivariate logistic regression, female gender (OR 3.5, 95% CI 1.2-10.3, $p=0.025$), increasing BMI (OR 1.1, 95% CI 1-1.1, $p=0.042$) and CRS (OR 4, 95% CI 1.5-10.9, $p=0.006$) were all independent risk factors for frequent exacerbations.

Symptom control

On univariate analysis, females had worse asthma control, as did patients with higher BMI, DB, OSA and GORD (Table 3).

On multivariate linear regression, both increasing BMI and DB were independent risk factors for poor asthma control.

Every unit increase in BMI resulted in a decrease in ACT score of 0.25 points (95% CI 0.12 – 0.37, $p<0.001$). Patients with DB had a mean ACT score which was 2.8 points (95% CI 0.7 – 5, $p=0.01$) lower than those without DB (Table 4).

Asthma quality of life

On univariate analysis, increasing BMI, and the presence of VCD, DB, OSA, or GORD predicted a poorer asthma quality of life (Table 3).

On multivariate linear regression, increasing BMI, the presence of VCD and DB were all independent predictors for poorer asthma quality of life.

For each unit increase in BMI, the AQLQ decreased by 0.05 points (95% CI 0.02 – 0.09, $p=0.006$). Patients with VCD had a mean AQLQ of 0.8 points (95% CI 0.2-1.4, $p=0.012$) lower than patients without VCD. Patients with DB had a mean AQLQ of 0.7 points (95% CI 0.1-1.3, $p=0.02$) lower than those without DB (Table 4).

Reanalysis of our data after excluding the 5 patients without asthma gave results which were largely unchanged. Female gender (OR 4.9, 95% CI 1.7-14.1, $p=0.003$) and presence of CRS (OR 3.9, 95% CI 1.4-10.6, $p=0.008$) remained as independent predictors of frequent exacerbations. Increasing BMI (B coefficient -0.23, 95% CI -0.35 to -0.1, $p=0.001$) and presence of dysfunctional breathing (B coefficient -2.53, 95% CI -4.77 to -0.31, $p=0.026$) were independent predictors of lower ACT score. Increasing BMI (B coefficient -0.05, 95% CI -0.09 to -0.01, $p=0.009$), presence of vocal dysfunction (B coefficient -0.82, 95% CI -1.44 to -0.2, $p=0.01$), and presence of dysfunctional breathing (B coefficient -0.73, 95% CI -1.37 to -0.1, $p=0.025$) were predictors of lower AQLQ. Only BMI as a predictor for frequent exacerbations fell below significance ($p=0.08$)

DISCUSSION

We showed that multiple comorbidities are independently associated with key asthma outcomes, even after adjustment for conventional parameters of FEV₁ and blood eosinophil count. Not only did these comorbidities constitute risk factors across all three domains of asthma outcomes, they appeared in our cohort to have a greater impact than conventional asthma parameters.

The magnitude of effect of comorbidities on asthma outcomes was clinically important. A patient with CRS was 4 times more likely to have frequent exacerbations compared to someone without CRS. The presence of DB decreased the ACT score by almost 3 points, which is the minimal clinically important difference (MCID) for this instrument in an individual.²² An increase in BMI by 10kg/m², the presence of DB and VCD all resulted in changes in AQLQ score exceeding the MCID of 0.5 points.²⁴

Obesity and asthma outcomes appear closely linked. The mechanisms relating obesity to asthma likely include mechanical factors, inflammatory mediators and altered immune responses.²⁵ Previous studies have identified obesity as an independent risk factor for poor asthma control.²⁶ Mosen et al²⁷ and Peters et al²⁸ have also shown an association between obesity, and increased exacerbations and quality of life. However none of these studies specifically examined the subgroup of difficult asthma patients. Cluster analysis of two carefully characterised severe asthma cohorts identified an ‘obese phenotype’ with high symptom burden²⁹ but there is considerably less data on the impact of obesity in the

heterogeneous group of difficult asthma patients. Our study further strengthens the observation that obesity is an important comorbidity in asthma.

Dysfunctional breathing comprises of abnormal chronic changes in breathing patterns that can lead to symptoms such as breathlessness or chest tightness.³⁰ Dysfunctional breathing affects a substantial proportion of patients with difficult asthma.⁵ One study of general asthma patients found worse asthma control scores in those with dysfunctional breathing.³¹ Dysfunctional breathing can lead to breathlessness disproportionate to airflow obstruction³² and an overestimation of the severity of asthma symptoms. The efficacy of breathing retraining on attenuating respiratory symptoms in asthma patients with dysfunctional breathing supports a causal association.³³ This provides plausible mechanism for our findings, in which presence of dysfunctional breathing worsened asthma control and quality of life.

In our study, CRS was an independent predictor of asthma exacerbations in patients with difficult asthma. This is concordant with a previous study¹⁴ among frequent exacerbators (OR 5.5, 95% CI 1.4-22.3). CRS has also been shown to be a risk factor for exacerbations in patients with less severe asthma.¹² Our findings support the hypothesis of the 'united airway disease'. This hypothesis proposes that upper and lower airway diseases are manifestation of a single inflammatory process within the respiratory tract. Therefore it is possible that the severity of disease in the upper airway parallels that in the lower airway.³⁴

VCD independently predicted poor asthma quality of life. VCD is now recognised to be a common finding among patients with difficult asthma³⁵ and associated with significant symptom burden.³⁶ VCD can also give rise to symptom misattribution.⁷ It has previously been suggested that asthma control was more difficult in patients with VCD³⁷ but overall, there is little available data on how VCD affects asthma outcomes.

Our results suggest that identifying the above comorbidities and understanding their impact on asthma outcomes should be an integral part of difficult asthma assessment. Timely recognition of these comorbidities is particularly important because treatments are readily available. Controlling these risk factors may potentially improve asthma symptoms and reduce exacerbations. There is evidence to suggest that weight loss³⁸, respiratory retraining for dysfunctional breathing³³ and treatment of CRS³⁹ can improve asthma outcomes. Importantly, failure to identify and treat these comorbidities may lead to unnecessary, and possibly ineffective, escalation of asthma treatment to expensive biologicals.

Undoubtedly, impaired lung function and the eosinophilic profile of asthma patients influence asthma outcomes.^{8, 9, 10} In our cohort, patients generally had a poor baseline lung function and patients with higher blood eosinophils had a trend towards increased exacerbations. Our observation that comorbidities appear to impact asthma outcomes to a more noticeable degree than lung function and blood eosinophils is probably due to the heterogeneity of our difficult asthma cohort, with many patients presenting with previously unrecognised and untreated comorbidities.

Our study has a number of strengths. To our knowledge, this is the first study to collectively assess the impact of all principal comorbidities across the spectrum of major asthma outcomes in a difficult asthma cohort. We included, and adjusted for, known asthma variables that might influence asthma outcomes. We demonstrated that the magnitude of effect on exacerbation frequency, ACT scores, and AQLQ scores in our study were clinically significant. Previous studies examining risk factors for poor asthma outcomes were conducted in non-difficult asthma cohorts.^{12, 13} The study conducted in a difficult asthma cohort in the Netherlands examined the impact of a selected number of comorbidities on only the single asthma outcome of exacerbation frequency.¹⁴

This study is attended by the usual constraints of cross-sectional analysis. First, we were unable to determine causality between identified risk factors and asthma outcomes. Second, prospective studies are needed to establish treatment effect of these risk factors on asthma outcomes. Third, our study cohort is drawn from a single-centre study with relatively few patients, decreasing the generalisability of our results. However, our findings are largely consistent with published data of difficult asthma patients.¹⁴ Lastly, we did not include risk factors such as medication adherence as we were unable to ascertain medication adherence objectively for all patients, and patient reported adherence is known to be inaccurate.⁴⁰

In conclusion, comorbidities are common in patients with difficult asthma. Increasing BMI, dysfunctional breathing, CRS, and VCD increase asthma exacerbations, worsen asthma control and impair asthma quality of life. Systematic evaluation for these conditions is therefore essential in difficult asthma. Our data highlights the need for prospective studies in

this challenging patient group to examine how addressing these comorbidities might improve asthma outcomes.

Disclosure Statement

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Accuracy of patient self-report as a measure of inhaled asthma medication use.

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Table 1: Baseline patient characteristics

Patient characteristics (n=90)	
Age, years	52±14
Gender, n (%)	
Female	58 (64.4%)
Race, n (%)	
White	83 (93.3%)
Duration of asthma, years	30±19
Smoking history, n (%)	
Never	48 (53.3%)
Ex-smoker	37 (41.1%)
Current	5 (5.6%)
Pre bronchodilator FEV ₁ , % predicted	67±23
Mean ICS dose (fluticasone equivalent), µg/d	864±465
Atopic status, n (%)	
Positive SPT or specific IgE to common aeroallergens	60 (66.7%)

Patients with absolute blood eosinophil ≥ 0.3 (10^9 cells/L), n (%)	38 (42.2%)
Exacerbations ≥ 3 /yr, n (%)	39 (43.3%)
Mean ACT score	14 $\pm$ 5
Mean AQLQ score	4.26 $\pm$ 1.45
Body Mass Index, kg/m ²	30.5 $\pm$ 8
Allergic Rhinitis, n (%)	40 (44.4%)
Chronic Rhinosinusitis, n (%)	32 (35.6%)
Gastroesophageal Reflux Disease, n (%)	21 (23.3%)
Obstructive Sleep Apnoea, n (%)	35 (38.9%)
Anxiety/depression, n (%)	28 (31.1%)
Dysfunctional Breathing, n (%)	27 (30%)
Vocal Cord Dysfunction, n (%)	29 (32.2%)

(ACT = Asthma Control Test, AQLQ = Asthma Quality of Life Questionnaire, FEV₁ =

Forced expiratory volume in 1 second, ICS = Inhaled corticosteroid, IgE = Immunoglobulin

E, SPT = Skin prick test)

Table 2: Comparison of characteristics of patients with ≥ 3 exacerbations/yr vs < 3 exacerbations/yr

	Exacerbations ≥ 3 /yr (n=39)	Exacerbations < 3 /yr (n=51)	P value
*Absolute blood eosinophil, 10^9 cells/L	0.37 $\pm$ 0.37	0.29 $\pm$ 0.29	0.276
Atopic status, n (%)	23 (59%)	37 (72.5%)	0.176
*Female gender, n (%)	32 (82.1%)	26 (51%)	0.02
*Age, years	49 $\pm$ 14	55 $\pm$ 14	0.043
*Duration of asthma, years	26 $\pm$ 17	33 $\pm$ 21	0.094
*Pre bronchodilator FEV ₁ , % predicted	70 $\pm$ 25	65 $\pm$ 22	0.409
Ever smoked, n (%)	16 (41%)	26 (51%)	0.348
*BMI, kg/m ²	33 $\pm$ 9	28 $\pm$ 7	0.008
AR, n (%)	16 (41%)	24 (47.1%)	0.568
*CRS, n (%)	20 (51.3%)	12 (23.5%)	0.006
GORD, n (%)	12 (30.8%)	9 (17.6%)	0.145

*OSA, n (%)	19 (48.7%)	16 (31.4%)	0.094
Anx/dep, n (%)	11 (28.2%)	17 (33.3%)	0.603
DB, n (%)	14 (35.9%)	13 (25.5%)	0.286
*VCD, n (%)	17 (463.6%)	12 (23.5%)	0.044

*Included as variables in multivariate analysis

(ACT = Asthma Control Test, AQLQ = Asthma Quality of Life Questionnaire, AR = Allergic rhinitis, BMI = Body mass index, CRS = Chronic rhinosinusitis, FEV₁ = Forced expiratory volume in 1 second, GORD = Gastroesophageal reflux disease, DB = Dysfunctional breathing, OSA = Obstructive sleep apnoea, VCD = Vocal cord dysfunction)

Table 3: Univariate analyses of risk factors for ACT and AQLQ

	ACT		AQLQ	
	B coefficient (95% CI)	P value	B coefficient (95% CI)	P value
* Absolute blood eosinophil, 10^9 cells/L	-0.97 (-3.472 to 3.277)	0.954	0.616 (-0.32 to 1.552)	0.194
Atopic status	-0.25 (-2.594 to 2.094)	0.833	0.407 (-0.25 to 1.063)	0.221
*Male Gender	2.952 (0.729 to 5.174)	0.01	0.243 (-0.402 to 0.889)	0.456
Age, year	-0.006 (-0.085 to 0.073)	0.885	-0.009 (-0.031 to 0.013)	0.436
Duration of asthma, years	0.024 (-0.033 to 0.081)	0.412	0.011 (-0.005 to 0.027)	0.168
* Pre-bronchodilator FEV ₁ , %	-0.008 (-0.055 to 0.04)	0.752	0.002 (-0.012 to 0.015)	0.794
Ever Smoked	0.143 (-2.072 to 2.358)	0.898	-0.044 (-0.67 to 0.583)	0.89
* BMI, kg/m ²	-0.266 (-0.393 to -0.14)	<0.001	-0.06 (-0.098 to -0.023)	0.002
AR	-0.435 (-2.657 to 1.787)	0.698	0.015 (-0.616 to 0.645)	0.963

CRS	-1.170 (-3.466 to 1.125)	0.314	0.072 (-0.585 to 0.728)	0.829
* GORD	-2.882 (-5.423 to -0.341)	0.027	-0.9 (-1.602 to -0.197)	0.013
* OSA	-2.400 (-4.609 to -0.191)	0.034	-0.69 (-1.325 to -0.074)	0.029
Anx/dep	-0.719 (-3.101 to 1.664)	0.55	-0.448 (-1.123 to 0.226)	0.19
* DB	-3.376 (-5.679 to -1.072)	0.005	-0.865 (-1.52 to -0.21)	0.01
* VCD	-2.388 (-4.698 to -0.078)	0.043	-0.952 (-1.587 to -0.316)	0.004

*Included in multivariate analysis for ACT

Included in multivariate analysis for AQLQ

(ACT = Asthma Control Test, AQLQ = Asthma Quality of Life Questionnaire, AR = Allergic rhinitis, BMI = Body mass index, CRS = Chronic rhinosinusitis, FEV₁ = Forced expiratory volume in 1 second, GORD = Gastroesophageal reflux disease, DB = Dysfunctional breathing, OSA = Obstructive sleep apnoea, VCD = Vocal cord dysfunction)

Table 4: Multivariate analyses for frequent exacerbations, ACT and AQLQ

Frequent exacerbations e3/year: Multivariate logistic regression			
Variables	Odds Ratio (OR)	95% CI	P value
Female	3.5	1.2 – 10.3	0.025
Increasing BMI	1.1	1 – 1.1	0.042
Chronic rhinosinusitis	4	1.5 – 10.9	0.006
ACT score: Multivariate linear regression			
Variables	B coefficients	95% CI	P value
Increasing BMI	-0.25	-0.37 to -0.12	<0.001
Dysfunctional breathing	-2.85	-5 to -0.7	0.01
AQLQ score: Multivariate linear regression			
Variables	B coefficients	95% CI	P value
Increasing BMI	-0.05	-0.09 to -0.02	0.006
Dysfunctional breathing	-0.73	-1.34 to -0.12	0.02
Vocal cord	-0.78	-1.38 to -0.18	0.012

dysfunction			
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(ACT = Asthma Control Test, AQLQ = Asthma Quality of Life Questionnaire, BMI = Body mass index)

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