

Factors Associated with Dysfunctional Breathing in Patients with Difficult to Treat Asthma



Eve Denton, MBBS(Hons), MPH, FRACP^{a,b}, Janet Bondarenko, B Physio^c, TunnRen Tay, MBBS, MRCP^a, Joy Lee, BHB, MBChB, FRACP^a, Naghmeh Radhakrishna, MBBS, FRACP^a, Fiona Hore-Lacy, BNutSci(Hons)^a, Catherine Martin, PhD^b, Ryan Hoy, MBBS, FRACP^{a,b}, Robyn O'Hehir, FAHMS, PhD, FRACP^{a,d}, Eli Dabscheck, MBBS, FRACP^a, and Mark Hew, MBBS, PhD, FRACP^{a,b} Melbourne, Victoria, Australia

What is already known about this topic? Dysfunctional breathing is an important treatable trait in difficult asthma. Little is known about why it arises, whom it afflicts, and who should be assessed.

What does the article add to our knowledge? This study found that dysfunctional breathing is present in almost 50% of patients with difficult asthma, and associated with poorer asthma status and control. Anxiety, depression, and sinonasal scores were independent risk factors for dysfunctional breathing.

How does the study impact current management guidelines? This study builds a profile of dysfunctional breathers in difficult asthma and highlights an important interaction between comorbid treatable traits.

BACKGROUND: Understanding of dysfunctional breathing in patients with difficult asthma who remain symptomatic despite maximal inhaled therapy is limited.

OBJECTIVE: We characterized the pattern of dysfunctional breathing in patients with difficult asthma and identified possible contributory factors.

METHODS: Dysfunctional breathing was identified in patients with difficult asthma using the Nijmegen Questionnaire (score >23). Demographic characteristics, asthma variables, and comorbidities were assessed. Multivariate logistic regression was performed for dysfunctional breathing, adjusted for age, sex, body mass index, and airflow obstruction.

RESULTS: Of 157 patients with difficult asthma, 73 (47%) had dysfunctional breathing. Compared with patients without dysfunctional breathing, those with dysfunctional breathing

experienced poorer asthma status (symptom control, quality of life, and exacerbation rates) and greater unemployment. In addition, more frequently they had elevated sino-nasal outcome test scores, anxiety, depression, sleep apnea, and gastroesophageal reflux. On multivariate analysis, anxiety (odds ratio [OR], 3.26; 95% CI, 1.18-9.01; $P = .02$), depression (OR, 2.8; 95% CI, 1.14-6.9; $P = .03$), and 22-item sino-nasal outcome test score (OR, 1.03; 95% CI, 1.003-1.05; $P = .03$) were independent risk factors for dysfunctional breathing.

CONCLUSIONS: Dysfunctional breathing is common in difficult asthma and associated with worse asthma status and unemployment. The independent association with psychological disorders and nasal obstruction highlight an important interaction between comorbid treatable traits in difficult asthma. © 2018 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2019;7:1471-6)

Key words: Asthma; Difficult asthma; Severe asthma; Treatable trait; Dysfunctional breathing; Breathing pattern disorder; Depression; Anxiety; Chronic rhinosinusitis

^aAllergy, Asthma & Clinical Immunology, The Alfred Hospital, Melbourne, Victoria, Australia

^bPublic Health & Preventive Medicine, Monash University, Melbourne, Victoria, Australia

^cPhysiotherapy Department, The Alfred Hospital, Melbourne, Victoria, Australia

^dDepartment of Medicine, Central Clinical School, Monash University, Melbourne, Victoria, Australia

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of Interest: The authors declare that they have no relevant conflicts of interest.

Received for publication August 30, 2018; revised November 1, 2018; accepted for publication November 19, 2018.

Available online December 7, 2018.

Corresponding author: Eve Denton, MBBS(Hons), MPH, FRACP, Respiratory Medicine, The Alfred Hospital, 55 Commercial Rd, Melbourne, Australia. E-mail: e.denton@alfred.org.au.

2213-2198

© 2018 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.jaip.2018.11.037>

INTRODUCTION

A subgroup of patients with asthma has difficult asthma, with uncontrolled disease despite maximal inhaled therapy. These patients experience significant morbidity, consume substantial health care resources, and present an ongoing clinical challenge.¹

Poor asthma control is manifested by residual symptom burden following treatment, but does not always correspond to the severity of airflow obstruction. One cause of disproportionate breathlessness in asthma is dysfunctional breathing, which is increasingly recognized but remains poorly understood.^{2,3} In

*Abbreviations used**HADS A and D- Hospital Anxiety and Depression Scale**OR- Odds ratio**QOL- Quality of life**VCD- Vocal cord dysfunction*

dysfunctional breathing, a disruption to the normal biomechanical pattern of breathing results in respiratory and non-respiratory symptoms.⁴ There are thought to be multiple different abnormal breathing patterns that fall under the umbrella of dysfunctional breathing including the most well-described, hyperventilation, but other forms include deep sighing, thoracic-dominant breathing, mouth breathing, accessory muscle use at rest, and thoraco-abdominal asynchrony. All are inefficient methods of breathing that can result in symptoms.⁵ Furthermore, these patterns of dysfunctional breathing have been shown to commonly overlap within the same patient.⁶ The presence of dysfunctional breathing can cause symptoms in patients with asthma who are unresponsive to escalation of asthma therapies but responsive to breathing retraining.⁶

The Nijmegen Questionnaire incorporates questions that cover 4 domains including symptoms related to the respiratory system, the peripheral and central neurovascular systems, and anxiety.⁷⁻¹¹ The questionnaire is able to distinguish adults with hyperventilation from healthy controls,^{7,12} and also remains the only validated tool to detect hyperventilation in the presence of asthma.¹³

We have previously reported the substantial presence of dysfunctional breathing in patients with difficult asthma.¹⁴ Dysfunctional breathing occurring at this end of the asthma spectrum may well exert the greatest clinical impact, but also yield the maximum therapeutic potential.

In this study, we therefore aimed to characterize the presence of dysfunctional breathing in a cohort with difficult asthma and to identify risk factors that may contribute to its development. We assessed patient demographic characteristics, asthma variables, and other comorbid treatable traits.

METHODS

Study design

We included consecutive adult patients who underwent systematic assessment for difficult asthma at our institution between June 1, 2014, and December 31, 2017, as previously described.¹⁵ Patients were referred to our difficult asthma program from specialist respiratory and allergy physicians with at least 1 of the following: severe or frequent asthma exacerbations despite treatment, inadequate control of asthma symptoms, unclear diagnosis, severe airflow obstruction, and/or complex management issues. These patients underwent a structured evaluation process comprising a standardized history, examination, adherence monitoring (via electronic monitoring device where possible),¹⁶ and a structured investigation process with the option for specific investigations and interventions based on clinical need. All patients evaluated via the program completed asthma and comorbidity questionnaires at baseline as well as lung function, skin prick testing, and other investigations as clinically indicated. Asthma diagnosis was based on the demonstration of variable airflow

obstruction via bronchodilator response, peak flow variability, and/or bronchoprovocation testing in the presence of a consistent clinical history. Asthma control was assessed via the 6-item Asthma Control Questionnaire, a validated questionnaire in asthma.¹⁷⁻¹⁹ Quality of life (QOL) was assessed via the Asthma Quality of Life Questionnaire.²⁰⁻²³

Ethics approval for this analysis was obtained from the Alfred Hospital Human Research Ethics Committee (approval reference no. 285/15) and requirement for specific informed consent was waived.

Patients were diagnosed with dysfunctional breathing if they had a positive Nijmegen Questionnaire defined by a score greater than 23 and accompanied by compatible clinical symptoms including excessive dyspnea.^{7,12} As with any questionnaire, the Nijmegen score has limitations including a variation in cutoff scores used for detecting the presence of dysfunctional breathing in different studies; for this reason, a sensitivity analysis was performed using the Nijmegen score as a continuous rather than dichotomous variable.

With regard to other comorbidities, psychiatric history was assessed by a history of clinical diagnosis and the Hospital Anxiety and Depression Scale (HADS A and HADS D), a questionnaire that has been validated to detect the presence of current anxiety and depression in an outpatient population.²⁴ A HADS A score of more than 11 signifies the presence of anxiety and a HADS D score of more than 8 signifies the presence of depression.²⁴ Atopy was defined by the presence of allergen specific IgE by a positive skin prick test result and/or positive serological testing to common aeroallergens. Allergic rhinitis diagnosis was based on clinical allergist diagnosis in the presence of atopy, and the level of symptom control was based on the Rhinitis Control Assessment Test, a validated questionnaire that assesses rhinitis-specific symptoms.²⁵ Chronic rhinosinusitis diagnosis was based on clinical symptoms with a positive computed tomography sinuses or compatible ear, nose, and throat specialist examination. Control of chronic rhinosinusitis symptoms was assessed using the validated sino-nasal outcome test score.²⁶ Obstructive sleep apnea was diagnosed on polysomnography. Gastroesophageal reflux diagnosis was based on compatible clinical symptoms plus an elevated Gastroesophageal Reflux Disease Questionnaire score of more than 2 or known history of gastroesophageal reflux disease on acid suppression medication. Vocal cord dysfunction (VCD) was diagnosed clinically by a specialist in VCD (ear, nose, and throat surgeon, speech pathologist, or respiratory physician) and supported by the Pittsburgh Index and the Vocal Cord Dysfunction Questionnaire. A subgroup of patients had the diagnosis confirmed by visualization of paroxysmal vocal fold motion on laryngoscopy.

Statistical methods

Nijmegen score was categorized, with a cutoff of more than 23 signifying the presence of dysfunctional breathing according to previously published data.^{7,27} Univariate and multivariate analyses were undertaken using logistic regression. Selected variables with *P* values of less than .1 were included in the logistic regression model to determine factors independently associated with dysfunctional breathing. In addition, a decision was made *a priori* to include sex, age, FEV₁ %predicted, and body mass index in the model regardless of *P* values on univariate analyses. Data were analyzed with SPSS Version 24 (IBM, Armonk, NY).

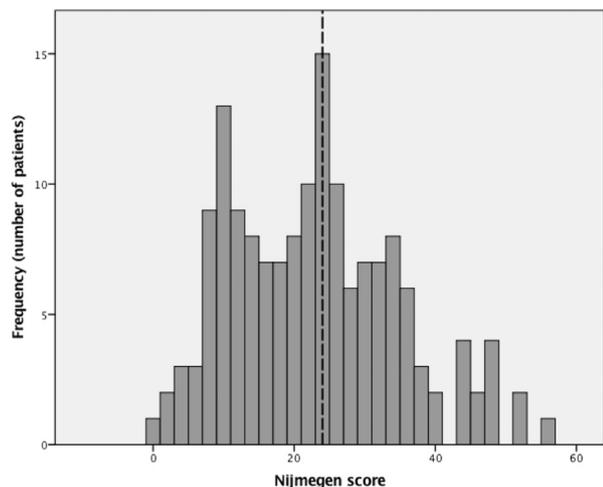


FIGURE 1. Distribution of Nijmegen questionnaire scores among patients with difficult asthma. The interrupted line indicates the cutoff score for dysfunctional breathing diagnosis

RESULTS

Patient characteristics

A total of 163 consecutive patients with difficult asthma underwent systematic assessment, of whom 157 completed Nijmegen questionnaires and were included for analysis, and the spread of Nijmegen scores is shown in Figure 1.

Among 157 included patients, the prevalence of dysfunctional breathing was 47% (73 of 157). The distribution of Nijmegen questionnaire scores showed a biphasic elevation, with peaks at 10 and 24 in what otherwise approximated a normal distribution. Baseline characteristics of the cohort are presented in Table I, stratified by the presence or absence of dysfunctional breathing. One hundred two were female (65%). Female patients had significantly higher mean Nijmegen questionnaire scores (24 vs 20; $P = .04$). Mean age was 52 ± 14 years ($n = 157$) and significantly different between the sexes: females 49 ± 14 years and males 56 ± 13 years ($P = .005$). There was no difference in mean age between those with and without dysfunctional breathing ($P = .7$). Only 52% of the cohort was employed and those with dysfunctional breathing were significantly less likely to be employed (44% vs 61%; $P = .04$).

Lung function and phenotype

There was no difference in FEV₁% predicted, total serum IgE, blood eosinophils, or fractional exhaled nitric oxide in those with and without dysfunctional breathing (Table I). Patients with the most severe degree of airflow obstruction (FEV₁% predicted <40%) had similar Nijmegen scores to those with less severe airflow obstruction (mean, 22.3 vs 22.5; $P = .95$).

Asthma control and QOL

As expected, baseline asthma control overall was poor, with mean number of severe exacerbations in the 6 months before review of 2.6 ± 2.1 and 6-item Asthma Control Questionnaire score of 2.4 ± 1.3 (Table I). Those with dysfunctional breathing had a significantly higher number of exacerbations in the 6 months before review (3 vs 2.5; $P = .037$) and a nonsignificant increase in reliever use in puffs per week (38 vs 27; $P = .17$). Those with

dysfunctional breathing also had worse asthma control (ACQ 6 2.8 vs 2.1; $P = .001$). Asthma-related QOL, measured by the Asthma Quality of Life Questionnaire, was worse in those with dysfunctional breathing (3.8 vs 4.6; $P < .001$).

Comorbidity diagnosis and control

Body mass index was elevated at baseline but did not differ significantly between those with and without elevated Nijmegen questionnaire scores ($P = .5$). Psychiatric comorbidity was frequent in the cohort, with 25% of patients having anxiety and 29% depression. Those with positive Nijmegen questionnaire scores had a significantly higher prevalence of comorbid anxiety (41% vs 11%; $P < .001$) and depression (44% vs 18%; $P = .001$). Similarly, there were higher HADS scores in those with positive Nijmegen questionnaire scores, HADS A (10 vs 5.3; $P < .001$) and HADS D (7.6 vs 3.6; $P < .001$) scores. Allergic rhinitis and chronic rhinosinusitis were not more frequent in those with dysfunctional breathing (Table I). However, symptom control scores were significantly worse with allergic rhinitis control, measured by Rhinitis Control Assessment Test (19 vs 22; $n = 151$; $P = .009$) and sinonasal symptom scores, measured by the 22-item sino-nasal outcome test (47 vs 32; $n = 155$; $P < .001$; minimum clinically important difference, 9). Obstructive sleep apnea (41% vs 24%; $n = 157$; $P = .02$) and gastroesophageal reflux disease (59% vs 35%; $n = 157$; $P = .002$) were significantly more frequent in those with dysfunctional breathing. VCD was not found more frequently in dysfunctional breathing (Table I).

Multivariate analysis

On multiple logistic regression, sinonasal symptoms (22-item sino-nasal outcome test, odds ratio [OR], 1.03; 95% CI, 1.003-1.05; $P = .03$), anxiety (OR, 3.26; 95% CI, 1.18-9.01; $P = .02$), and depression (OR, 2.8; 95% CI, 1.14-6.9; $P = .03$) were all independent risk factors for dysfunctional breathing (Table II).

Results were similar when analysis was performed using Nijmegen questionnaire score as a continuous rather than as a dichotomous variable (data not shown).

DISCUSSION

Given the extremely high prevalence of dysfunctional breathing in this cohort with difficult asthma—of almost 50%—there is a profound need to enhance detection and treatment of dysfunctional breathing. In this study, patients with dysfunctional breathing had poorer asthma status and unemployment, which are key patient outcomes. Dysfunctional breathing was also independently predicted by anxiety, depression, and uncontrolled sinonasal disease, suggesting an important interaction between multiple comorbid treatable traits (Figure 2). These findings offer potential mechanistic insights and novel treatment avenues for dysfunctional breathing.

Breathlessness is common in patients with difficult asthma, and this breathlessness may sometimes be disproportionate to the degree of airway pathology.⁴ Dysfunctional breathing is a common but underrecognized cause of excessive breathlessness in this population, and is important to identify due to the potential for treatment.²⁸ Breathing retraining in those with mild to moderate asthma improves QOL and symptoms,²⁹ and recent data from our group suggest similar benefits in more severe asthma.⁶ It is possible that all patients with difficult asthma may derive benefit from breathing retraining regardless of Nijmegen questionnaire

TABLE 1. Baseline characteristics of patients with difficult asthma (n = 157), comparing those with (Nijmegen questionnaire score >23) and without dysfunctional breathing

Characteristic	Difficult asthma (n = 157)	No dysfunctional breathing (n = 84)	With dysfunctional breathing (n = 73)	P value
Demographic				
Age (y), mean ± SD	52 ± 14	52 ± 16	51 ± 12	.7
Female sex, n (%)	102 (65)	51 (61)	51 (70)	.23
Employed, n (%)	82 (52)	51 of 84 (61)	31 of 70 (44)	.04
Smoker, n (%)				
Never	88 (56)	52 of 84 (62)	36 of 73 (49)	.25
Ex	61 (39)	27 of 84 (32)	34 of 73 (47)	
Current	7 (4.5)	4 of 84 (5)	3 of 73 (4)	
Asthma variables, mean ± SD				
Asthma duration (y)	30.4 ± 19	31 ± 17	29 ± 20	.52
FEV ₁ (% predicted)	67 ± 22.2	67.6 ± 22	65.7 ± 22	.6
Blood eosinophils (10 ⁹ /L)	0.34 ± 0.36	0.33 ± 0.36	0.46 ± 1.1	.32
FENO (ppb), n = 132	33 ± 28	31 ± 25	34 ± 30	.46
Serum total IgE (kU/L)	515 ± 1010	500 ± 1034	532 ± 988	.84
Exacerbations in previous 6 mo	2.6 ± 2.1	2.3 ± 1.9	3 ± 2.3	.04
Reliever use (puffs per week)	32 ± 49	27 ± 41	38 ± 57	.17
Six-item Asthma Control Questionnaire	2.4 ± 1.3	2.1 ± 1.2	2.8 ± 1.3	.001
Asthma Quality of Life Questionnaire	4.2 ± 1.3	4.6 ± 1.2	3.8 ± 1.2	<.001
Comorbidities				
Obesity, n (%)	82 (52)	41 of 84 (49)	41 of 73 (56)	.36
BMI (kg/m ²), mean ± SD	31.4 ± 8.3	30.9 ± 8.9	31.9 ± 7.6	.5
Chronic rhinosinusitis, n (%)	63 of 157 (40)	36 of 84 (43)	27 of 73 (37)	.45
SNOT-22 score, mean ± SD	39 ± 21	32 ± 19	47 ± 20	<.001
Allergic rhinitis, n (%)	82 of 157 (52)	45 of 84 (54)	37 of 73 (51)	.7
RCAT, mean ± SD	21 ± 5.1	22 ± 4.8	19 ± 5.3	.009
Anxiety—clinical diagnosis, n (%)	39 of 130 (30)	14 of 69 (20)	25 of 61 (41)	.01
Anxiety HADS A score > 11, n (%)	38 of 154 (25)	9 of 83 (11)	29 of 71 (41)	<.001
Depression—clinical diagnosis, n (%)	44 of 130 (34)	17 of 69 (25)	27 of 61 (44)	.02
Depression HADS D score > 8, n (%)	46 of 155 (30)	15 of 84 (18)	31 of 71 (44)	<.001
VCD—clinical diagnosis, n (%)	58 of 157 (37)	27 of 84 (32)	31 of 73 (43)	.18
VCD on laryngoscopy, n (%)	25 of 157 (16)	13 of 84 (16)	12 of 73 (16)	.87
Gastro-oesophageal reflux, n (%)	72 of 157 (46)	29 of 84 (35)	43 of 73 (59)	.002
Obstructive sleep apnea, n (%)	50 of 157 (32)	20 of 84 (24)	30 of 73 (41)	.02

BMI, Body mass index; FENO, fractional exhaled nitric oxide; ppb, parts per billion; RCAT, Rhinitis Control Assessment Test; SNOT-22, 22-item sino-nasal outcome test. Bold indicates statistical significance ($P < .05$).

score. However, in resource-limited environments, review of all patients by a specialist physiotherapist is not feasible and a method of identifying patients who may benefit most is important.

The first key finding in this study was that psychiatric disease is independently associated with dysfunctional breathing among patients with difficult asthma. This association has long been suspected even though previous evidence has been scarce.³⁰⁻³³ After adjusting for multiple variables, patients with difficult asthma with dysfunctional breathing were 3.3 times more likely to have anxiety and 2.8 times more likely to have depression than those without dysfunctional breathing. These are important findings, not least because these conditions are potentially treatable. Other data from our center have revealed that breathing retraining improves Nijmegen questionnaire scores but has no effect on HADS scores. This suggests that psychiatric disease should be specifically addressed alongside breathing retraining in those with both conditions.⁶

The second key finding on multivariate analysis was that patients with difficult asthma with dysfunctional breathing were more likely to have elevated sinonasal scores. This association is biologically plausible, as uncontrolled nasal congestion could be leading to mouth breathing, itself a form of dysfunctional breathing.^{30,34} Therefore, assiduous attention to treating sinonasal comorbidities may well be important to reduce dysfunctional breathing symptoms. Indeed, a previous longitudinal report from our center found that improvements in both sinonasal scores and Nijmegen questionnaire scores could be achieved through active targeting of comorbidities in difficult asthma.³

Comorbidities in difficult asthma are considered to be an important bundle of treatable traits, each of which may impact asthma control.^{3,35} The data from this study support the hypothesis that interactions may also occur *between* these comorbid treatable traits.³ It is possible that clusters of such comorbidities may exert a combined effect on asthma outcomes, and this area requires further study.

TABLE II. Multivariate analysis for dysfunctional breathing

Variable	OR	95% CI	P value
Male sex	0.85	0.35-2.07	.71
Age	0.98	0.95-1.01	.17
FEV ₁ (% predicted)	0.98	0.96-1.01	.14
Body mass index	1.003	0.95-1.06	.91
Exacerbations in previous 6 mo	1.1	0.9-1.35	.34
Six-Item Asthma Control Questionnaire	1.05	0.63-1.78	.84
Asthma Quality of Life Questionnaire	0.96	0.55-1.67	.87
Anxiety score on Hospital Anxiety and Depression Scale	3.26	1.18-9.01	.02*
Depression score on Hospital Anxiety and Depression Scale	2.8	1.14-6.9	.03*
22-Item sino-nasal outcome test	1.03	1.003-1.05	.03*
Obstructive sleep apnea	1.78	0.69-4.58	.24
Gastroesophageal reflux disease	1.96	0.82-4.69	.13

*P < .05.

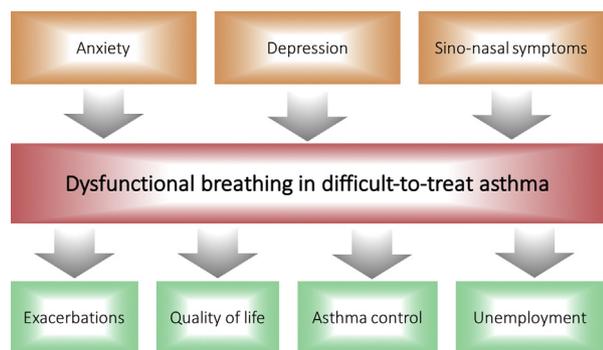


FIGURE 2. A proposed paradigm of associations and consequences of dysfunctional breathing in difficult asthma

On univariate analysis, patients with dysfunctional breathing in our cohort experienced significantly more asthma exacerbations requiring oral corticosteroids. They also had worse asthma control and QOL. The difference between Asthma Quality of Life Questionnaire scores in those with positive Nijmegen questionnaire score compared with negative Nijmegen questionnaire score was statistically and clinically significant (0.93; minimal clinically important difference, 0.5). Thus, the potential benefit of identifying and treating dysfunctional breathers among patients with difficult asthma may be substantial.

In this cohort, no association was found between lung function impairment and elevated Nijmegen questionnaire scores. We specifically examined the subset of patients with the most severe airways obstruction, who might be postulated to have a higher likelihood of breathlessness due to organic disease. However, their Nijmegen questionnaire scores were no different from the scores of those without severe airways obstruction. Similarly, inflammatory biomarker levels such as total serum IgE, atopic status, and serum eosinophils were unrelated to Nijmegen questionnaire scores. These results highlight the need to investigate for dysfunctional breathing in all patients with difficult asthma regardless of lung function impairment or inflammatory phenotype.

We found that those with dysfunctional breathing were significantly less likely on univariate analysis to be employed,

an important finding given the relatively young population and the economic implications. Similar to previous data, we found an association between younger age and the presence of dysfunctional breathing. Unlike other studies we found no correlation between the presence of dysfunctional breathing and sex.³⁶

There was no statistically significant association found between the presence of dysfunctional breathing and VCD. It is possible that this association was underestimated because of our strict diagnostic criteria for VCD requiring patients to have either undergone laryngoscopy or been diagnosed by a specialist in this area. However, not all patients underwent laryngoscopy or were reviewed by VCD specialists.

We used the presence of an elevated Nijmegen questionnaire score to indicate the presence of dysfunctional breathing. Although the Nijmegen questionnaire score has limited utility as a diagnostic tool, it remains the only validated method of diagnosing dysfunctional breathing in patients with asthma. In the absence of a criterion standard diagnosis, this is the most widely used and practical diagnostic tool. Although data were collected prospectively, the analysis was performed retrospectively and this could lead to information bias. This was an uncontrolled study and suffers from the lack of an appropriately matched control group.

In conclusion, dysfunctional breathing affects almost half the patients with difficult asthma. It is independently associated with anxiety, depression, and poorer upper airway scores, highlighting an interaction between comorbid treatable traits. These data highlight the importance of addressing dysfunctional breathing in difficult asthma, and may offer enhanced diagnostic and treatment strategies.

REFERENCES

1. Israel E, Reddel HK. Severe and difficult-to-treat asthma in adults. *N Engl J Med* 2017;377:965-76.
2. Radhakrishna N, Tay TR, Hore-Lacy F, Stirling R, Hoy R, Dabscheck E, et al. Validated questionnaires heighten detection of difficult asthma comorbidities. *J Asthma* 2017;54:294-9.
3. Tay TR, Hew M. Comorbid “treatable traits” in difficult asthma: current evidence and clinical evaluation. *Allergy* 2017;73:1369-82.
4. Depiazzi J, Everard ML. Dysfunctional breathing and reaching one’s physiological limit as causes of exercise-induced dyspnoea. *Breathe* 2016;12:120-9.
5. Boulding R, Stacey R, Niven R, Fowler SJ. Dysfunctional breathing: a review of the literature and proposal for classification. *Eur Respir Rev* 2016; 25:287-94.
6. Denton E, Bondarenko J, O’Hehir RE, Hew M. Breathing pattern disorder in difficult asthma: characteristics and improvement in asthma control and quality of life after breathing re-training. *Allergy* 2019;74:201-3.
7. van Dixhoorn J, Folgering H. The Nijmegen Questionnaire and dysfunctional breathing. *ERJ Open Res* 2015;1:00001-2015.
8. Courtney R, van Dixhoorn J, Greenwood KM, Anthonissen EL. Medically unexplained dyspnea: partly moderated by dysfunctional (thoracic dominant) breathing pattern. *J Asthma* 2011;48:259-65.
9. Han JN, Schepers R, Stegen K, Van den Bergh O, Van de Woestijne KP. Psychosomatic symptoms and breathing pattern. *J Psychosom Res* 2000;49: 319-33.
10. Homsveld H, Garssen B. Hyperventilation syndrome: an elegant but scientifically untenable concept. *Netherlands J Med* 1997;50:13-20.
11. Prys-Picard CO, Kellett F, Niven RM. Disproportionate breathlessness associated with deep sighing breathing in a patient presenting with difficult-to-treat asthma. *Chest* 2006;130:1723-5.
12. van Dixhoorn J, Duivenvoorden HJ. Efficacy of Nijmegen Questionnaire in recognition of the hyperventilation syndrome. *J Psychosom Res* 1985;29: 199-206.
13. Grammatopoulou EP, Skordilis EK, Georgoudis G, Haniotou A, Evangelodimou A, Fildissis G, et al. Hyperventilation in asthma: a validation study of the Nijmegen Questionnaire-NQ. *J Asthma* 2014;51:839-46.

14. Radhakrishna N, Tay TR, Hore-Lacy F, Hoy R, Dabscheck E, Hew M. Profile of difficult to treat asthma patients referred for systematic assessment. *Respir Med* 2016;117:166-73.
15. Tay TR, Lee J, Radhakrishna N, Hore-Lacy F, Stirling R, Hoy R, et al. A structured approach to specialist-referred difficult asthma patients improves control of comorbidities and enhances asthma outcomes. *J Allergy Clin Immunol Pract* 2017;5:956-964.e3.
16. Lee J, Ren Tay T, Radhakrishna N, Hore-Lacy F, Mackay A, Hoy R, et al. Non-adherence in the era of severe asthma biologics and thermoplasty. *Eur Respir J* 2018;51. pii: 1701836.
17. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902-7.
18. Jia CE, Zhang HP, Lv Y, Liang R, Jiang YQ, Powell H, et al. The Asthma Control Test and Asthma Control Questionnaire for assessing asthma control: systematic review and meta-analysis. *J Allergy Clin Immunol* 2013;131:695-703.
19. Juniper EF, Svensson K, Mörk A-C, Ståhl E. Measurement properties and interpretation of three shortened versions of the Asthma Control Questionnaire. *Respir Med* 2005;99:553-8.
20. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax* 1992;47:76.
21. Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. Measuring quality of life in asthma. *Am Rev Respir Dis* 1993;147:832-8.
22. Mölken MP, Custers F, Doorslaer E, Jansen CCM, Heurman L, Maesen FPV, et al. Comparison of performance of four instruments in evaluating the effects of salmeterol on asthma quality of life. *Eur Respir J* 1995;8:888-98.
23. Rowe BH, Oxman AD. Performance of an Asthma Quality of Life Questionnaire in an outpatient setting. *Am Rev Respir Dis* 1993;148:675-81.
24. Law M, Naughton MT, Dhar A, Barton D, Dabscheck E. Validation of two depression screening instruments in a sleep disorders clinic. *J Clin Sleep Med* 2014;10:683-8.
25. Schatz M, Meltzer EO, Nathan R, Derebery MJ, Mintz M, Stanford RH, et al. Psychometric validation of the rhinitis control assessment test: a brief patient-completed instrument for evaluating rhinitis symptom control. *Ann Allergy Asthma Immunol* 2010;104:118-24.
26. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clin Otolaryngol* 2009;34:447-54.
27. Vansteenkiste J, Rochette F, Demedts M. Diagnostic tests of hyperventilation syndrome. *Eur Respir J* 1991;4:393.
28. Holloway EA, West RJ. Integrated breathing and relaxation training (the Papworth method) for adults with asthma in primary care: a randomised controlled trial. *Thorax* 2007;62:1039-42.
29. Bruton A, Lee A, Yardley L, Raftery J, Arden-Close E, Kirby S, et al. Physiotherapy breathing retraining for asthma: a randomised controlled trial. *Lancet Respir Med* 2018;6:19-28.
30. Agache I, Ciobanu C, Paul G, Rogozea L. Dysfunctional breathing phenotype in adults with asthma—incidence and risk factors. *Clin Transl Allergy* 2012;2:18.
31. Mora JD, Grant L, Kenyon P, Patel MK, Jenner FA. Respiratory ventilation and carbon dioxide levels in syndromes of depression. *Br J Psychiatry* 2018;129:457-64.
32. Stevenson I, Ripley HS. Variations in respiration and in respiratory symptoms during changes in emotion. *Psychosom Med* 1952;14:476-90.
33. Gardner WN. The pathophysiology of hyperventilation disorders. *Chest* 1996;109:516-34.
34. Bartley J. Nasal congestion and hyperventilation syndrome. *Am J Rhinol* 2005;19:607-11.
35. Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, et al. Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J* 2016;47:410.
36. Thomas M, McKinley RK, Freeman E, Foy C. Prevalence of dysfunctional breathing in patients treated for asthma in primary care: cross sectional survey. *BMJ* 2001;322:1098-100.