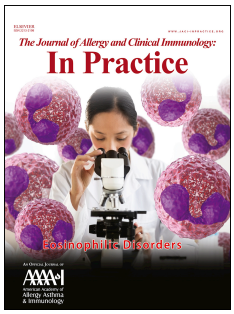

Associations of Breathing Pattern Disorder and Nijmegen Score with Clinical Outcomes in Difficult-to-treat Asthma

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Title: Associations of Breathing Pattern Disorder and Nijmegen Score with Clinical Outcomes in Difficult-to-treat Asthma

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Professor Peter Howarth reports employment by GSK outside of the submitted work. Dr. Adnan Azim and Clair Barber report employment from Astra Zeneca outside of the submitted work. Anna Freeman, Steevo Abraham, Latha Kadalayil, Judit Varkonyi-Sepp, Ben Ainsworth, JJ Hudson-Colby, Clair Barber, Paddy Dennison, Adnan Azim, Heena Mistry, Peter Howarth, Ratko Djukanovic, Hongmei Zhang, Hasan Arshad, Hans Michael Haitchi, and Ramesh Kurukulaaratchy declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

ACQ6: Asthma Control Questionnaire, BEC: Blood eosinophil count, BMI: Body mass index, BPD: breathing pattern disorder, BRC: Biomedical Research Centre, CI: confidence interval, COPD: Chronic Obstructive Pulmonary Disease, FeNO: Fractional Exhaled Nitric Oxide, FEF: Forced Expiratory Flow rate, FEV1: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity, GINA: Global Initiative for Asthma, GORD: Gastroesophageal reflux disease, HADS-A: Hospital Anxiety and Depression Score-Anxiety, HADS-D: Hospital Anxiety and Depression Score-Depression, IgE: immunoglobulin E, ICU: Intensive Care Unit, ILO: Inducible Laryngeal Obstruction, MARS: Medication Adherence Report Scale, MEF, Mid expiratory flow, NIHR: National Institute for Health and Care Research, NQ: Nijmegen Questionnaire, OCS: Oral CorticoSteroids, OSA: Obstructive sleep Apnoea, REC: Research Ethics Committee, SD: Standard Deviation, SGRQ: St George's Respiratory Questionnaire, SPT: Skin Prick Test, UHSFT: University Hospital Southampton Foundation Trust, WATCH: Wessex AsThma CoHort of Difficult Asthma.

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Abstract

Background

Breathing pattern disorder (BPD) reflects altered biomechanical patterns of breathing that drive breathing difficulty and commonly accompanies difficult-to-treat asthma. Diagnosis of BPD has no gold standard, but Nijmegen Questionnaire (NQ) >23 is commonly used.

Objectives

We sought to advance clinical characterisation of BPD and better understand clinical utility of NQ in difficult asthma, in patients from the Wessex AsThma CoHort of difficult asthma (WATCH) study.

Methods

Association between demographic and clinical factors in difficult asthma and BPD, ascertained by clinical diagnosis (yes/no, n=476), by NQ scores (≤23: normal (no suggestion of BPD) and >23: abnormal (suggested BPD), n=372, as well as the continuous raw NQ scores) were assessed in univariate models to identify significant risk factors associated with the three BPD outcomes. For the clinician-diagnosed and NQ-based BPD, associations of continuous factors were assessed using independent samples t-test or Mann-Whitney U test as appropriate for the data distribution or by Spearman correlation test. Dichotomous associations were evaluated using chi-squared tests. Multivariable logistic (dichotomous outcomes) and linear regression models (continuous outcomes) were developed to identify predictive factors associated with clinician-diagnosed and NQ-based BPD, dichotomous and continuous. Patients with data on NQ scores were grouped into NQ quartiles (low,

moderate, high, and very high). The patterns of association of the quartiles with four health-related questionnaire outcomes were assessed using linear regression analyses.

Results

Multivariable regression identified that clinically diagnosed BPD was associated with female sex (OR 1.85; 95% CI 1.07, 3.20), comorbidities (rhinitis (OR 2.46; 95% CI 1.45, 4.17), GORD (OR 2.77; 95% CI 1.58, 4.84), ILO (OR 4.37; 95% CI 2.01, 9.50) and any psychological co-morbidity (OR 1.86; 95% CI 1.13, 3.07)) and healthcare usage (exacerbations (OR 1.07; 95% CI 1.003, 1.14) and previous ICU admissions (OR 2.03; 95% CI 1.18, 3.47)). Abnormal NQ-based BPD diagnosis was associated with history of eczema (OR 1.83; 95% CI 1.07, 3.14), GORD (OR 1.94; 95% CI 1.15, 3.27) or any psychological comorbidity (OR 4.29; 95% CI 2.64, 6.95) at multivariable regression. Differences between clinical and NQ-based BPD traits were also found with 42% discordance in BPD-state between these definitions. Multivariable linear regression analysis with NQ as a continuous outcome showed positive association with worse asthma outcomes (admission to ICU, p=0.037), different phenotypic traits (female sex p=0.001, ever smoker, p=0.025)) and greater multimorbidity (GORD, p=0.002, sleep apnoea, p=0.040, any psychological comorbidity, p<0.0001).

Conclusion

BPD is associated with worse health outcomes and negative health impacts in difficult asthma within a multimorbidity disease model. It therefore merits better recognition and prompt treatment. Clinical diagnosis and NQ offer different perspectives on BPD, so this goal may be best addressed by considering clinical features alongside magnitude of NQ.

Highlights box (35 words each question)

What is already known about this topic? Breathing pattern disorder is common in difficult asthma and is associated with worse outcomes. There is no gold standard to diagnose BPD but NQ questionnaire score >23 and clinical diagnosis are commonly used.

What does this article add to our knowledge? NQ and a clinical diagnosis of BPD identify differing phenotypes of difficult asthma and are not always concordant. NQ as a continuous and categorical variable is associated with worsening clinical outcomes in difficult asthma.

How does this study impact current management guidelines? BPD has significant negative impact in difficult asthma and merits better diagnosis and treatment. Diagnosis should ideally incorporate both clinical features and NQ, while NQ as a categorical scoring tool may also aid clinical understanding.

Key words. A list of up to 10 key words should follow the Highlights Box

Breathing-pattern-disorder (BPD), Nijmegen questionnaire (NQ), multimorbidity, difficult asthma, treatable trait

Introduction

Breathing Pattern Disorder (BPD) or dysfunctional breathing describes a spectrum of breathing disorders(1), characterized by alteration in normal biomechanical patterns of breathing that drive consequent breathing difficulty(2). It often coexists with chronic respiratory disease like asthma, but can also occur secondary to other cardiopulmonary conditions or even in the absence of concurrent disease. With no universal gold standard definition for BPD, timely diagnosis may be challenging. Assessment of BPD is often supported by the Nijmegen Questionnaire (NQ), originally validated to identify hyperventilation, using a cut-off score of 23 as abnormal(3). In mild-to-moderate asthma, the NQ has been validated for screening hyperventilation, but not for a broader diagnosis of BPD(4). Furthermore, there are limitations to using a dichotomised NQ to assess BPD in patients with asthma. These include capture of overlapping symptoms to asthma, arbitrary nature of discrete cut-off values for abnormality and focus on select profiles (hyperventilation) of BPD.

Difficult-to-treat ("difficult") asthma is defined as asthma that is uncontrolled despite GINA (Global Initiative for Asthma) Step 4 or 5 treatment(5) or requires such treatment to maintain good control and reduce exacerbations. It includes most patients with complex asthma(6, 7) and is responsible for a disproportionately high burden of asthma-associated disability and healthcare costs(8). Difficult asthma is increasingly recognised as a multidimensional condition associated with numerous comorbidities that merit targeted treatment approaches(9). These "treatable traits" frequently combine into a multimorbidity disease framework (defined as coexistence of ≥2 long-term health conditions) that collectively imposes significant patient burden. BPD is one highly prevalent comorbidity in

difficult asthma, occurring in 24-47% patients(10-13). In difficult asthma, BPD has been associated with significantly worse asthma control and quality of life, and more frequent asthma exacerbations(12). The contribution of BPD to acute healthcare needs in difficult asthma is not well described; nor are patient-level impacts such as asthma treatment needs, working ability and psychological distress. Better understanding of how BPD links to multimorbidity in difficult asthma could facilitate more holistic and effective multidisciplinary treatment approaches(14).

An NQ cut-off of >23 was used to define BPD in previous difficult asthma studies (11). Whether a continuous measure interpretation of NQ in difficult asthma could help better identify BPD, understand associated health-risks and target BPD-focused interventions appropriately merits attention. Assessment of BPD in difficult asthma by a broader clinical diagnosis could assist clinicians in better recognising BPD, as could understanding how NQ-based and clinical diagnoses of BPD align or differ in such patients.

We hypothesized that different diagnostic strategies for BPD would show differences in detection and characteristics of BPD plus associated comorbidities, multimorbidity and clinical outcomes. We also hypothesized that the magnitude of NQ (measured continuously or as categories rather than as a simple binary variable) will be associated with worse difficult asthma outcomes regardless of BPD diagnosis. In the largest study to date of BPD in difficult asthma, our aims were:

1. To advance clinical characterisation of BPD in difficult asthma diagnosed
    a. By clinician

b. By dichotomous NQ groups (abnormal or normal)

2. To understand whether clinical diagnosis and NQ should be used independently or in conjunction, by exploring concordance in BPD status defined by these 2 approaches.
3. To investigate whether NQ as a continuous or categorical measure reveals a severity gradient of associated features in patients with difficult asthma.

Methods

Enrolment data were analysed from 500 well-characterized participants within the WATCH study, described in(15), with Difficult Asthma defined for this study as patients attending the Adult or Transitional Regional Asthma Clinic at University Hospital Southampton Foundation Trust (UHSFT) or satellite outreach clinics on the Isle of Wight who are managed with "high dose therapies" and/or "continuous or frequent use of oral corticosteroids", according to the BTS Adult Asthma Management Guidelines 2019. The study design and protocol has been approved by West Midlands- Solihull Research Ethics Committee (REC reference: 14/WM/1226)(15)

This study focuses on patients with data on clinical diagnosis of BPD (n=476) and NQ score data (n=372) collected at WATCH enrolment. The clinical diagnosis of BPD was made by the Asthma Specialist Physician in the difficult asthma clinic. It involved a composite diagnosis by an experienced Severe Asthma Specialist, based on detection of characteristic clinical features such as breathlessness, sighing, chest pain, "air hunger" (a sense of being unable to get a complete breath in even after a maximal inspiratory manoeuvre), tingling, dizziness, and general fatigue obtained from the medical history, alongside clinical observation/examination findings during the consultation. Symptoms of hyperventilation at WATCH enrolment were assessed using NQ with score >23 considered abnormally raised

and consistent with an NQ-based BPD diagnosis. A cut off of 23 was chosen as this is the value that is most widely used clinically in asthma, and has been used in prior studies in relation to difficult and severe asthma(11, 13). Asthma symptoms at enrolment were assessed using the Asthma Control Questionnaire (ACQ6). Probable psychological distress was also determined at enrolment via the Hospital Anxiety and Depression Score (HADS) Questionnaire(16). Medication Adherence Report Scale (MARS) scores were used to assess medication adherence(17). Quality of life was measured at enrolment using the St George's Respiratory Questionnaire (SGRQ) (18). Permissions to use any copyrighted questionnaires in the clinical/ research setting were obtained, where required, for the purposes of the WATCH study(15). Objective measures recorded at enrolment included anthropometry, allergy skin prick test (SPT), fractional exhaled nitric oxide (FeNO), spirometry (forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC], FEV_1/FVC and mid-expiratory flow [$FEF_{25–75}$]), plus highest blood eosinophil count (BEC) and highest Total IgE in the preceding 10-years. Health care utilization was captured through number of oral corticosteroid (OCS) courses, number of hospitalisations in the preceding 12 months, and ever needing intubation and ventilation for acute asthma. Comorbidities were diagnosed by clinicians in the clinic using conventional criteria. Multimorbidity was defined by cumulative rank reflecting number of additional diagnosed comorbidities additive to asthma.

Statistical Analysis

Statistical analysis was conducted using SPSS software (Statistical Product and Service Solutions) version 26 IBM Corp, NY, USA), GraphPad Prism version 6, (GraphPad Software, California, USA) and Stata 17 SE (StataCorp, Texas, USA). To address our aims, 5 sets of comparisons were performed:

1. Difficult asthma patients with and without clinical diagnosis of BPD (n=476).
2. Difficult asthma patients with and without abnormal NQ (>23) (n=372).
3. Assessment of concordance in BPD status based on abnormal/normal NQ (>23) and no/clinical BPD diagnosis for participants where both were available (n= 357).
4. Characterization of difficult asthma patients using a continuous measure of NQ.
5. Characterization of multiple categories of NQ with quartile-based cut-offs; low (≤12), moderate (13-21), high (22-31) and very high (≥32).

We first carried out univariate analyses to identify potentially informative factors for inclusion in subsequent multivariable linear or logistic regression models. Factors, considered likely relevant for BPD in difficult asthma patients, were tested for their association with three BPD outcomes - clinician-diagnosed (dichotomous: yes/no), NQ score-based (dichotomous (normal: ≤23 and abnormal: >23)) and raw NQ scores (continuous). Associations of these factors with the BPD outcomes listed above were evaluated using t-test/Mann-Whitney U test (continuous factors) or chi-squared test (dichotomous factors). Spearman correlation test was used to estimate correlation between continuous factors and raw NQ scores. The comorbidities tested in univariate analyses were obesity, rhinitis, eczema, gastro-oesophageal reflux disease (GORD), inducible laryngeal obstruction (ILO), psychological (anxiety and/or depression), sulphite sensitivity, salicylate sensitivity, sleep apnoea, Chronic Obstructive Pulmonary Disease (COPD) and bronchiectasis (non-cystic fibrosis).

Next, we developed multivariable regression models to identify risk factors associated with the three BPD outcomes. Predictors with p-values <0.1 in the univariate analyses were included in the initial multivariable logistic (clinician-diagnosed and NQ score-based

dichotomous BPD outcomes) or linear (raw NQ scores) regression models. A stepwise backward variable elimination was employed for model selection. The non-significant factor (p-value >0.05) with the highest p-value was excluded from the initial model to obtain the next model. The process was repeated until all factors included in the model were with a more stringent p-values <0.05.

NQ quartiles were generated using the 'xtile' command of Stata 17.0 SE. The significance level was set at 5% unless otherwise specified.

Results

Characteristics Associated with a Clinical Diagnosis of BPD

Data for analysis regarding clinical diagnosis of BPD were available in 476/500 enrolled WATCH participants, among whom the prevalence of clinically diagnosed BPD was 48.7%. In univariate analyses, patients with clinically diagnosed BPD were significantly younger (median: 50 vs 55-years, p <0.001), more often female and had younger age of asthma onset **(Table 1, Comparison A**). Clinically diagnosed BPD was associated with greater healthcare utilisation. Significantly greater prevalence of several comorbidities **(Figure 1A)** and different distributions (higher burden) of multimorbidity **(Table 1, Comparison A)** occurred with clinical diagnosis of BPD. Clinical diagnosis of BPD was also associated with significantly worse asthma control (ACQ6), quality of life (SGRQ), and probable psychological distress (HADS) (**Table 1, Comparison A)**. Associations between clinical diagnosis of BPD and Body Mass Index (BMI)/obesity (BMI>30), smoking history, other clinical comorbidities, need for biological treatment, spirometry or biological markers such as blood eosinophil count and Total IgE did not achieve pre-defined statistical significance **(Table 1, Comparison A and Supplementary Table E1).**

Multivariable logistic regression found that females were more likely to have been clinically diagnosed as having BPD (**Table 2, Group A**). Odds of BPD diagnosis decreased with age, but considerably increased in those with rhinitis (2.5-fold), GORD (2.8-fold), ILO (4.4-fold), psychological comorbidities (86% higher), or lifetime history of having asthma-related admissions to ICU (doubled). Asthma exacerbations in the year prior to enrolment contributed to a small increase (7%) in the risk of a clinical diagnosis of BPD.

Characteristics Associated with an NQ-based BPD Diagnosis

Data on NQ status were available for 372 participants of whom 42.5% had an abnormal NQ (>23, suggestive of BPD). When classifying BPD status by NQ>23, significant differences were found between participants with normal and abnormal NQ scores (**Table 1, Comparison B**). As for clinical diagnosis of BPD, females were more likely to have an abnormal NQ. However, unlike for clinical diagnosis, asthma patients who were obese (BMI>30), or those who smoked were also found to have abnormal NQ. Increased OCS use was found in those with abnormal NQ. Patients with abnormal NQ also had significantly higher prevalence of several comorbidities **(Figure 1B)** and different distribution (higher burden) of multimorbidity than those with normal NQ **(≤23, Table 1, Comparison B)**. As with clinical diagnosis, NQ-based diagnosis of BPD was associated with significantly worse asthma control (ACQ6), quality of life (SGRQ), and probable psychological distress (HADS) **(Table 1, Comparison B).** There were no significant differences in other demographic and clinical characteristics (**Table 1, Comparison B)** or objective measures including spirometry, FeNO, BEC, Total IgE or atopic status **(Supplementary Table E2)**.

Eczema, GORD, psychological comorbidity (anxiety, depression or both) and salicylate sensitivity were identified as predictors of NQ-based diagnosis of BPD based on NQ>23 in multivariable logistic regression analysis **(Table 2, Group B).**

Concordance of Clinical and NQ-based BPD Diagnosis

Data were available for both clinical and NQ-based BPD status for 357 participants. Concordant refers to agreement in the presence or absence of BPD in patients by both clinical diagnosis and NQ-based assessment. Discordant refers to the disagreement between the two BPD assessment modalities. Among these 357 participants, 58.5% showed concordance of BPD status for clinical and NQ-based definitions. One fifth (22.7%) had a clinical diagnosis of BPD but NQ≤23 while a similar proportion (18.8%) had NQ>23 but no clinical diagnosis of BPD **(Table 3**). Descriptive features of the respective concordant/ discordant BPD groups are provided in **Supplementary Table E3**.

Characterization of Continuous Measure NQ in Difficult Asthma

Clinical characteristics of the WATCH enrolment cohort were assessed by continuous measure NQ in 372 participants. Significantly higher NQ was found in females, obese, those who had ever smoked and those hospitalized for acute asthma in univariate analysis (**Table 4**). Significant associations were found between higher NQ and higher BMI, comorbid eczema, GORD, ILO, any psychological comorbidity, salicylate sensitivity and sleep apnoea, number of courses of OCS for asthma in the 12-months prior to enrolment, and worse post-BD FEV_1/FVC, asthma control (ACQ6), quality of life (SGRQ), probable psychological distress (HADS-A/D)**.** Multimorbidity level was significantly associated with higher NQ score.

Multivariable linear regression found that increasing continuous measure NQ was associated with female sex, history of smoking, GORD, psychological comorbidity, sleep apnoea and lifetime history of having asthma ICU admission **(Table 2, Group C).**

Characterization of NQ quartiles in Difficult Asthma

NQ data were categorised using quartiles into low (≤12), moderate (13-21), high (22-31) and very high NQ score (≥32). Compared to the reference group of low NQ (≤12), there were common associations across other quartiles such that those with low scores were less likely to be female, have higher HADS-A and D scores, lower Quality of Life (SGRQ) scores and greater symptom burden (higher ACQ6) **(Figure 2 and Supplementary Table E4)**. As the NQ score increased through moderate to very high, the number of comorbidities associated with each group increased **(Supplementary Table E4).** Symptom burden, as measured by ACQ6, increased by 0.63, 0.96 and 1.62 in moderate, high and very high NQ quartiles compared to the low category of NQ ≤12 (reference group) (Figure 2). All increased ACQ6 scores were greater than the minimal clinically important difference (MCID) of 0.5. There were also worse probable psychological comorbidity outcomes as assessed by HADS (A and D) scores. For example, HADS-A and HADS-D scores increased by 8.56 and 7.31 scores respectively, on a scale of 0-21, in the very high NQ quartile compared to the reference quartile (low), suggesting increased anxiety and depression for the individuals in the very high group compared to those in the reference group. Considerable worsening of QoL was also seen as assessed by SGRQ (scores) which increased by 34.69 points, on a scale of 0-100, compared to the reference group). Overall, increasing NQ score category was associated with worsening of asthma control (ACQ6), quality of life (SGRQ), psychological status (HADS-A and -D) **(Figure 2)**.

Discussion

This paper demonstrates that current isolated assessments of BPD are not sufficient or concordant for diagnosis, and a more specific and nuanced assessment is needed. We confirm and extend existing literature characterising BPD in difficult asthma, with demonstration that BPD in difficult asthma is associated with a younger age of asthma onset, female sex, anxiety and depression, upper airway pathology and smoking (11, 13). Additionally, we show poorer outcomes associated with a clinical diagnosis of BPD in the context of difficult asthma, with association between BPD and hospital and ICU admission, rescue oral corticosteroid courses and lost workdays, highlighting the individual and health economic need to address BPD. The observed lack of association with more objective markers of asthma severity (spirometry, FeNO, peripheral BEC) have been variably reported previously in the literature(11, 13). We demonstrate different clinical insights if BPD is diagnosed clinically or by high NQ score. Multimorbidity was significantly associated with BPD diagnosed by either NQ or clinical diagnosis when compared to the respective groups with no BPD diagnosis, reinforcing the importance of addressing multimorbidity in difficult asthma **(summarised in Figure 3).**

Current diagnostic tools (NQ) are not validated for BPD diagnosis in difficult asthma. We demonstrate, for the first time, that association patterns differ in some respects between the two existing approaches of BPD diagnosis, namely NQ>23-based and a clinical diagnosis of BPD. Nevertheless, female sex, greater health care utilisation and worsening asthma control, quality of life and psychological comorbidities were all associated with both NQ>23-based (plus continuous measure of NQ) and clinical-based diagnosis of BPD. Additionally, we showed, for the first time, that multimorbidity in asthma is associated with both binary NQ

score-based and a clinical diagnosis of BPD. However, several other associations such as with BMI, obesity, history of smoking and exacerbations needing OCS were detected only by the NQ score method. These findings further highlight the need for a more comprehensive diagnostic approach for BPD diagnosis combining clinical assessment and questionnaire assessment.

We demonstrate considerable discordance between a clinical assessment and NQ score >23 for diagnosis of BPD which suggests that neither is independently sufficient or objective to diagnose BPD. This may be in part due to the NQ detecting breathlessness and symptoms related to asthma or other cardiopulmonary diseases rather than BPD; obesity is a good example of this with changes in lung volumes and additional weight contributing to shortness of breath that may be incorrectly identified as hyperventilation/BPD by the NQ but has a physiological basis. Additionally, some of this discordance may relate to symptom perception; similar to a seminal cluster analysis of inflammatory and clinical phenotypes in asthma, which demonstrated concordance or lack thereof in differing clusters between disease severity in asthma and symptom burden(19). This may additionally translate across to BPD and be reflected in the discordant groups described herein, whereby patients with a low NQ score do not perceive their symptoms of BPD as the clinician diagnosing BPD. Similarly to subjective questionnaire scores, clinical BPD diagnosis is also based on subjective clinician interpretation of symptoms, and even if the clinician is observing behaviours/symptoms those are often influenced by psychological processes. The Breathing Pattern Assessment Tool under development may go some way to addressing this but remains unvalidated(20). In the meantime, the need for more comprehensive approach to diagnosis of BPD is emphasised by our findings. It is noteworthy that symptoms of BPD may

401 be misattributed to asthma with consequent overestimation of asthma severity,
402 inappropriate over-medication of asthma but limited improvement in symptom control(13).
403 Conversely, treating BPD with breathing retraining exercises can significantly improve
404 symptoms and quality of life (21-23), highlighting the importance of identifying and
405 appropriately treating this comorbidity in difficult asthma(15).
406
407 Given neither NQ as a binary measure or clinical BPD diagnosis are validated or comparable
408 as a measure of BPD and are associated with different clinical outcomes, we sought to
409 explore whether NQ as a continuous measure was of greater utility as a diagnostic tool. NQ
410 as a continuous variable shows positive correlation with increasing exacerbations, worse
411 symptom and quality of life scores and greater probable psychological distress, highlighting
412 the clinical utility of the continuous NQ score as a tool for assessing BPD severity, potentially
413 for triage of referrals for physiotherapy and multimorbidity management. Historically,
414 different cut-offs for NQ score have been proposed and used in clinical practice(4, 24). We
415 demonstrate for the first time that there is a gradient of severity associated with increasing
416 NQ score and its associations with difficult asthma outcomes. We further demonstrate that
417 utilising NQ severity categories retains this adverse outcome gradient, with worsening
418 symptom burden, quality of life and higher anxiety and depression progressing through the
419 increasing Nijmegen quartiles. Following validation in other cohorts, this would be
420 immediately translatable to clinical practice, for example to triage referrals to physiotherapy
421 led breathing retraining or to monitor response to breathing retraining and to trigger
422 consideration for assessment and management of psychological factors.
423

The use of NQ as a continuous score is not directly informative in terms of guiding clinical management in routine clinical practice, and so we sought to simplify this approach for clinical use through categorical characterisation of NQ. We demonstrate that categorically ranked NQ adds novel insight to aid clinicians. Those in the highest NQ group were more likely to be female, have higher BMI, ever smoked, needed more OCS courses, ever been intubated, been hospitalised in the previous 12 months, had depression, anxiety, GORD, ILO or OSA. Additionally, linear regression analysis demonstrated statistically significant worsening of ACQ6, SGRQ, HADS-A and -D with increasing NQ categorisation compared to the reference group of low NQ, highlighting groups that may benefit most in terms of targeted treatment of BPD and offering a potential tool for triage of patients in need of breathing retraining, and response to this.

There are both strengths and limitations to this work. The diagnosis of BPD was present at time of study enrolment when NQ was recorded but does not consider effects of any preceding breathing retraining that may have been provided. This may have accounted for some discordance between diagnostic modalities. We acknowledge that our study presents a large number of univariate statistical analyses in order to characterise the phenotypic traits and associated health outcomes for the different BPD definitions. This might raise concerns for false discovery implications. However, our univariate analyses were used to identify variables for entry into multivariable regression analyses and those adjusted findings were the focus for main outcomes in this paper. The WATCH cohort is predominantly a white British cohort, and it remains to be seen whether these findings are translatable to other ethnic groups. However, the WATCH cohort is a large and well characterised group of patients covering a wide geographical area(15), providing a wealth of

448 data on comorbidities and health questionnaire outcomes. There are few studies
449 investigating BPD in difficult asthma and the data presented herein is the largest cohort to
450 look at this.
451
452 In summary, this is the largest study of BPD in difficult asthma to date and serves to support
453 and extend existing knowledge around the deleterious association of BPD with asthma
454 outcomes. This work creates clinically useful new insights, that better define the phenotype
455 of BPD within a multimorbidity model of difficult asthma. Additionally, it highlights the
456 utility of NQ gradient in clinical practice and the need to consider a broader definition of
457 BPD in clinical practice. However, the discordance between NQ and clinical diagnosis of BPD
458 suggests that relying on NQ alone gives limited perspective and therefore may miss
459 diagnoses where patients would benefit from treatment. A comprehensive assessment for
460 BPD should be considered within the wider context of multimorbidity in all patients with
461 difficult asthma. Future work should focus on developing measures to both aid better
462 recognition of BPD in patients with difficult asthma but also to further develop effective and
463 easily accessible treatments that mitigate the negative impact of BPD on patients with
464 difficult asthma.

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Figure 1: (A) Statistically significant comorbidities with a higher prevalence (>5%) in patients with a clinical diagnosis of BPD, assessed by Chi-squared tests. and (**B**) Significant comorbidities with a higher prevalence in patients with a raised Nijmegen score, assessed by Chi-squared tests. Abbreviations: BPD; breathing pattern disorder, GORD: Gastroesophageal reflux disease, ILO: Intermittent Laryngeal Obstruction
* (p-value<0.05); ** (p-value<0.01); *** (p-value<0.001)

Figure 2: Linear Regression Analysis of NQ score categorised as low, moderate, high, and very high. The plot has been split into two sections for clarity and to accommodate the differing X-axis scales. Abbreviations ACQ6: Asthma Control Questionnaire 6 (range well controlled 0-6 poorly controlled); NQ: Nijmegen Questionnaire, SGRQ: St George's Respiratory Questionnaire (range best health 1-100 poor health), HADS: Hospital Anxiety and Depression Score (range no anxiety/depression 0-21 high levels of anxiety/depression). Low (comparator) Nijmegen score ((≤12), moderate Nijmegen score (13-21), high Nijmegen score (22-31) and very high Nijmegen score (>31). NQ quartiles were generated using the 'xtile' command of Stata 17.0 SE.

Figure 3: Summary figure demonstrating novel findings from this paper. Both clinical diagnosis and Nijmegen Score > 23 are used to diagnose BPD in difficult asthma. Continuous and categorical use of the NQ scores add additional insight into associations of BPD and difficult asthma. BPD is associated with increasing co- and multimorbidity in difficult asthma. Abbreviations: BPD: breathing pattern disorder, GORD Gastroesophageal reflux disease, ICU: Intensive Care Unit

Table 1. Comparison of clinical characteristics of patients with and without Breathing Pattern Disorder (BPD) based on (**A**) clinical diagnosis or (**B**) Nijmegen score.

Clinical factors		**A: Clinical diagnosis**			**B: Nijmegen score**		
	Overall (N = 500)	**No BPD (N = 244)**	**BPD (N = 232)**	**P-value**	**Normal (≤23) (N = 214)**	**Abnormal (>23)* (N = 158)**	**P-value**
Age at enrolment (years)				**<0.0001**			**0.188**
Median (IQR)	52 (38.5, 63)	55 (44, 65)	50 (34, 60)		52 (37, 64)	50.5 (38, 61	
Number analysed	500	244	232		214	158	
Gender, n (%)				**0.010**			**0.008**
Male	174 (34.8)	99 (40.6)	68 (29.3)		88 (41.1)	44 (27.8)	
Female	326 (65.2)	145 (59.4)	164 (70.7)		126 (58.8)	114 (72.2)	
Age of asthma onset, (years)							
Median (IQR)	19.0 (4.0, 40.0)	22.0 (6.0, 45.0)	16.5 (3.0, 35)	**0.015**	20.0 (6.0, 43.0)	15.5 (3.0, 35.0)	0.073
Number analysed	478	233	222		207	150	
Body Mass Index (BMI)							
Median (IQR)	29.7 (25.6, 33.9)	29.3 (25.5, 33.9)	30.1 (25.9, 36.1)	0.185	28.2 (24.8, 32.8)	30.3 (26.5, 36.1)	**0.001**
Number analysed	494	242	229		213	155	
Ever Smoked, n (%)	238 (47.7)	115 (47.1)	11 (49.6)	0.697	90 (42.3)	87 (55.1)	**0.015**
Number analysed	499	244	231		213	158	
Number of OCS Course(s) during the 12 months prior to enrolment							
Median (IQR)	3 (1, 5)	2 (1, 4)	3 (1, 6)	**0.008**	2 (1, 5)	3 (1, 5)	**0.016**

Number analysed	448	225	205		198	142	
Ever been to ICU, n (%)	141 (28.3)	52 (21.3)	83 (35.9)	**0.038**	53 (24.8)	52 (32.9)	0.084
Number analysed	499	244	231		214	158	
Hospitalizations in the last 12 months, n (%)							
Ever been hospitalized	144 (29.0)	57 (23.5)	79 (34.5)	**0.008**	50 (23.5)	50 (32.1)	0.067
Number analysed	496	243	229		213	156	
Number of days lost (work/educations) in the last 12 months							
Median (IQR)	5.0 (0, 20.0)	3.0 (0, 14.0)	8.5 (0, 30)	**0.009**	4.0 (0, 20.0)	5.0 (0, 20.0)	0.785
Number analysed	270	134	122		133	83	
Questionnaire Outcomes							
ACQ6							
Median (IQR)	2.5 (1.5, 3.5)	2.2 (1.2, 3.0)	2.8 (2.0, 3.8)	**<0.0001**	2.0 (1.0, 2.8)	3.2 (2.3, 3.8)	**<0.0001**
Number analysed	466	230	212		208	154	
SGRQ (total)							
Median (IQR)	51.1 (35.2, 67.3)	47.2 (30.6, 64.0)	55.0 (43.2, 70.1)	**0.0001**	40.0 (24.9, 52.2)	66.5 (52.6, 75.1)	**<0.0001**
Number analysed	380	193	170		175	132	
HADS (anxiety)							
Median (IQR)	6.0 (3.0, 10.0)	5.5 (3.0, 9.0)	7.0 (4.0, 12.0)	**0.0001**	4.0 (2.0, 6.0)	10.0 (7.0, 14.0)	**<0.0001**
Number analysed	424	208	195		201	147	
HADS (depression)							
Median (IQR)	4.0 (2.0, 8.0)	4.0 (2.0, 7.0)	5.0 (2.0, 9.0)	0.063	3.0 (1.0, 5.0)	8.0 (5.0, 11.0)	**<0.0001**
Number analysed	425	209	195		200	147	

MARS-A10							
Median (IQR)	4.6 (3.9, 9.0)	4.8 (4.0, 9.0)	4.6 (3.9, 9.0)	0.472	4.6 (4.0, 5.0)	4.4 (3.8, 5.0)	0.274
Number analysed	500	244	232		214	158	
Multimorbidity level¶							
Median (IQR)	3 (2, 4)	3 (2, 4)	4 (3, 5)	**<0.0001**	3 (2, 4)	4 (3, 5)	**<0.0001**
Number analysed	372	201	168		169	110	

BPD and no-BPD (clinical diagnosis) and Abnormal and Normal (Nijmegen scores) were compared using chi-squared test when reported as proportions or using Mann-Whitney test when reported as medians of their distribution. Number analysed not reported when data were available for all patients.

IQR: inter quartile range (25%, 75%); OCS: oral corticosteroids, ICU: intensive care unit, ACQ6: Asthma Control Questionnaire 6; SGRQ: St George's Respiratory Questionnaire, HADS: Hospital Anxiety and Depression Score: MARS-A10: Medication Adherence Report Scale

*Nijmegen score of >23 (Abnormal) suggests high likelihood of BPD.

¶Multimorbidity levels were generated using the eleven most prevalent (>5%) co-morbidities reported in WATCH cohort based on patients with complete data on all ten comorbidities (n=372). The comorbidities included were obesity, rhinitis, eczema, gastro-oesophageal reflux disease (GORD), inducible laryngeal obstruction (ILO), psychological (anxiety and/or depression), sulphite sensitivity, salicylate sensitivity, sleep apnoea, COPD and bronchiectasis (non-cystic fibrosis).

15 **Table 2:** Factors associated with clinician-diagnosed (**A**) and Nijmegen score-based ascertainment (**B**

16 **& C**) of breathing pattern disorder (BPD)

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A: Clinician-diagnosed BPD* (N = 351)†			
Factors	**n/351**	**Odds Ratio¥ (95% CI)**	**P-value**
Age at enrolment (in decades)	351	0.79 (0.67, 0.94)	**0.008**
Gender (F vs M)	F/M: 226/125	1.85 (1.07, 3.20)	**0.028**
History of rhinitis (Y vs N)	Y/N: 123/228	2.46 (1.45, 4.17)	**0.001**
Diagnosed with GORD (Y vs N)	Y/N: 234/117	2.77 (1.58, 4.84)	**<0.0001**
Diagnosed with ILO (Y vs N)	Y/N: 48/303	4.37 (2.01, 9.50)	**<0.0001**
Any psychological comorbidity (Y vs N)¶	Y/N: 156/195	1.86 (1.13, 3.07)	**0.014**
Exacerbations†	351	1.07 (1.003, 1.14)	**0.038**
Ever been admitted to ICU (Y vs N)	Y/N: 103/248	2.03 (1.18, 3.47)	**0.010**
B: Nijmegen score (>23 vs ≤23) (N = 325) †**			
Factors	**n/325**	**Odds Ratio¥ (95% CI)**	**P-value**
History of eczema (Y vs N)	Y/N: 87/238	1.83 (1.07, 3.14)	**0.028**
Diagnosed with GORD (Y vs N)	Y/N: 215/110	1.94 (1.15, 3.27)	**0.013**
Any psychological comorbidity (Y vs N)¶	Y/N: 149/176	4.29 (2.64, 6.95)	**<0.0001**
Salicylate sensitivity	Y/N: 246/79	1.89 (1.08, 3.32)	**0.026**
C: Nijmegen score (continuous)€ (N = 322) †			
Factors	**n/322**	**Coefficient# (95% CI)**	**P-value**
Gender (F vs M)	F/M: 207/115	4.36 (1.77, 6.95)	**0.001**
Smoker ever (Y vs N)	Y/N: 155/167	2.83 (0.36, 5.30)	**0.025**
Diagnosed with GORD (Y vs N)	Y/N: 213/109	4.06 (1.53, 6.59)	**0.002**
Any psychological comorbidity (Y vs N)¶	Y/N: 146/176	8.00 (5.47, 10.53)	**<0.0001**
Sleep apnoea ever (Y vs N)	Y/N: 27/295	4.55 (0.22, 8.95)	**0.040**
Ever been admitted to ICU (Y vs N)	Y/N: 89/233	2.84 (0.17, 5.50)	**0.037**

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Linear and logistic regressions were carried out using the predictors, including comorbidities, with p-values <0.1 in the univariate analyses for the three types of BPD outcomes. Factors with P-values<0.05 after regression analyses are shown in bold. CI: confidence interval; F: female; M: male; Y: yes; N: no; GORD: gastro-oesophageal reflux disease; ILO: inducible laryngeal obstruction; OCS: oral corticosteroids; ICU: intensive care unit.

*BPD as binary outcome (Yes vs No), analysed using logistic regression

†Numbers with complete data for the final model for each of the outcomes

¥Odds ratio: fold/percentage change in risk associated with a unit change in the factor being considered (e. g. change associated with a change in 10 years of age)

¶Psychological comorbidity includes anxiety only, depression only or both anxiety and depression

§Exacerbations needing OCS in the 12 months before enrolment

**Nijmegen score of >23 was used to ascertain the presence of BPD. Factors associated with BPD were identified by logistic regression.

€Nijmegen score (0-64) used for ascertaining BPD (continuous data), analysed using linear regression

#Coefficient = change in Nijmegen score associated with a unit change in the factor being considered (e. g. change from male to female)

Table 3 Prevalence of patients concordant/discordant for Nijmegen scores (NQ) > 23 and clinical diagnosed breathing pattern disorder (BPD)

	NQ > 23	**Clinical Diagnosed BPD**	**Patients**	**Prevalence (%)**
Concordant	Yes	Yes	N = 85	24
	No	No	N = 124	35
Discordant	Yes	No	N = 67	19
	No	Yes	N = 81	23
Total			N = 357	100

Abbreviations: Numbers (N); Percentage (%). NQ = Nijmegen score, BPD = Breathing Pattern Disorder.

Table 4: Comparison of clinical characteristics of patients using Nijmegen score as a continuous outcome

Clinical factors	**Nijmegen score (N=372)**	
Dichotomous clinical factors		
	Median (IQR)	**P-value**
Gender		**0.0002**
Male (n=132)	17.0 (9.0, 27.0)	
Female (n=240)	23.0 (14.5, 32.0)	
Obesity		**0.022**
Not obese (BMI≤30, n=198)	20.0 (12.0, 29.0)	
Obese (BMI >30, n=170))	23.0 (13.0, 33.0)	
Ever Smoked		**0.002**
No (n=194)	19.0 (11.0, 29.0)	
Yes (n=177)	23.0 (16.0, 33.0)	
Ever been to ICU		0.082
No (n=267)	21.0 (12.0, 31.0)	
Yes (n=105)	23.0 (13.0, 34.0)	
Hospitalisations in the last 12 months		**0.027**
No (n=269)	21.0 (12.0, 30.0)	
Yes (n=100)	23.5 (15.0, 34.0)	

Eczema ever		0.077
No	21.0 (12.0, 30.0)	
Yes	24.0 (13.0, 32.0)	
GORD		<0.0001
No	16.0 (9.0, 25.0)	
Yes	23.0 (15.0, 33.0)	
ILO		0.033
No	21.0 (12.0, 30.0)	
Yes	28.0 (21.0, 36.0)	
Any psychological comorbidity		<0.0001
No	17.0 (10.0, 25.0)	
Yes	24.0 (18.0, 32.0)	
Salicylate sensitivity		0.053
No	21.0 (12.0, 30.0)	
Yes	24.0 (13.0, 34.0)	
Sleep Apnoea ever		0.001
No	21.0 (12.0, 30.0)	
Yes	30.5 (22.0, 34.0)	
Other clinical factors		

	Correlation coefficient¶	**P-value**
Age at enrolment (year), (n=372)	-0.09	0.078
Age of Asthma Onset (years), (n=372)	-0.07	0.172
BMI (n=368)	0.17	**0.001**
Number of OCS course(s) count in the last 12 months (n=340)	0. 15	**0.005**
Work/education days lost in the last 12 months (n= 216)	0.12	0.08
Multimorbidity levels§ (n = 279)	0.36	**<0.0001**
Lung function (spirometry measurements, % predicted¥)		
FEV1 (n=269)	0.05	0.374
FVC (n=268)	-0.08	0.212
FEV1/FVC (n=268)	0.128	**0.036**
MEF25-75 (n=269)	0.10	0.112
FeNO# (n=306)	-0.04	0.454
Questionnaire outcomes		
ACQ6 ((n=362)	0.47	**<0.0001**
SGRQ (symptoms) (n=362)	0.48	**<0.0001**

SGRQ (activity) (n=327)	0.55	**<0.0001**
SGRQ (impacts) (n=314)	0.64	**<0.0001**
SGRQ (total) (n=307)	0.64	**<0.0001**
HADS (anxiety) (n=348)	0.72	**<0.0001**
HADS (depression) (n=347)	0.62	**<0.0001**
HADS (total) (n=342)	0.74	**<0.0001**
MARS-A10 (n=372)	-0.05	0.381

[¶]Spearman correlation coefficient

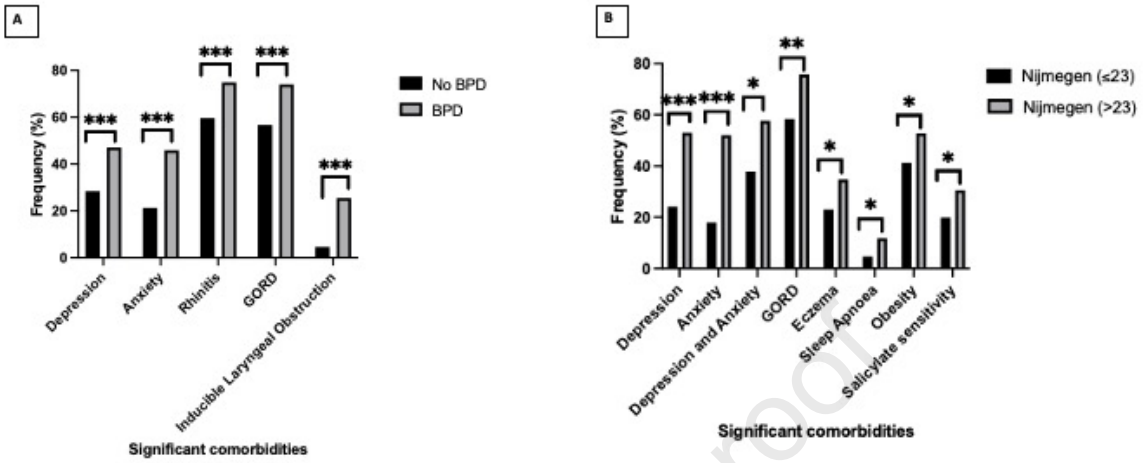
[§]Multimorbidity levels were generated using ten most prevalent (>5%) comorbidities reported in WATCH cohort based on patients with complete data on all ten comorbidities (n=372). The comorbidities included were obesity, rhinitis, eczema, gastro-oesophageal reflux disease (GORD), inducible laryngeal obstruction (ILO), psychological (anxiety and/or depression), sulphite sensitivity, salicylate sensitivity, sleep apnoea, COPD and bronchiectasis (non-cystic fibrosis).

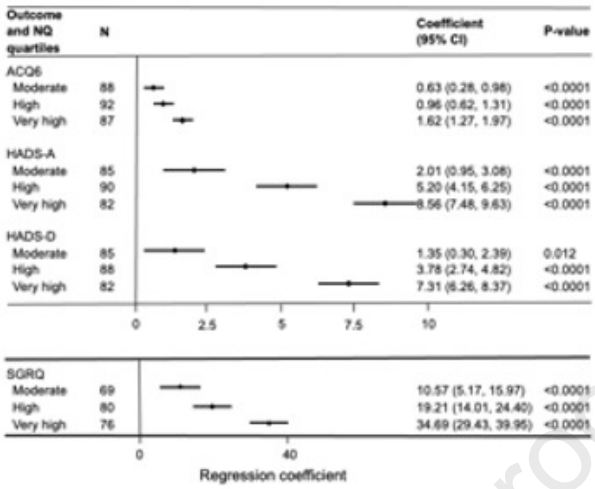
[¥]Post-bronchodilator (BD) values presented

[#]Measured using Bedfont NO breath mouthpiece exhaled at 50 ml/sec

Median Nijmegen scores of the categories were compared for the dichotomous factors. For the continuous lung function measures and questionnaire outcomes the association with Nijmegen scores were evaluated using Spearman correlation coefficients. Abbreviations: BMI: body mass index; IQR: inter quartile range (25%, 75%); ICU: intensive care unit; OCS: oral corticosteroids; FEV1: forced expiratory volume (litres/sec); FVC: forced vital capacity in unit (litres)**;**

MEF_{25-75} : ratio of MEF_{25-75} to vital capacity; FeNO: fractional inhaled nitric oxide at expiratory rate of 50ml/s in parts per billion (ppb); ACQ6: Asthma Control Questionnaire 6; SGRQ: St George's Respiratory Questionnaire, HADS: Hospital Anxiety and Depression Score: MARS-A10: Medication Adherence Report Scale.





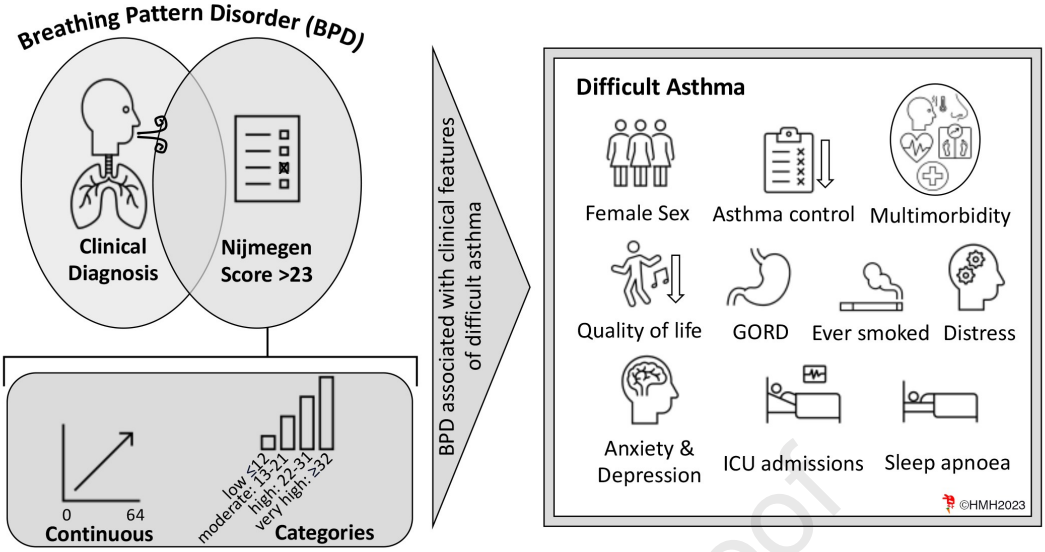


Figure 3