Official Journal of the Asian Pacific Society of Respirology
Respirology

ORIGINAL ARTICLE

Treatable traits can be identified in a severe asthma registry and predict future exacerbations

VANESSA M. MCDONALD,[1] SARAH A. HILES,[1] KRYSTELLE GODBOUT,[2] ERIN S. HARVEY,[1,3] GUY B. MARKS,[4,5] MARK HEW,[6] MATTHEW PETERS,[7] PHILIP G. BARDIN,[8] PAUL N. REYNOLDS,[9,10] JOHN W. UPHAM,[11,12] MELISSA BARAKET,[13] ZAHEERODIN BHIKOO,[14] JEFFREY BOWDEN,[15] BEN BROCKWAY,[16] LI PING CHUNG,[17] BELINDA COCHRANE,[18,19] GLORIA FOXLEY,[5] JEFFREY GARRETT,[20] LATA JAYARAM,[21,22] CHRISTINE JENKINS,[7,23,24,25] CONSTANCE KATELARIS,[19,26] GREGORY KATSOULOTOS,[27] MARIKO S. KOH,[28,29] VICKY KRITIKOS,[30,31] MARINA LAMBERT,[32] DAVID LANGTON,[33,34] ALEXIS LARA RIVERO,[27] PETER G. MIDDLETON,[35,36,37] ALDOPH NANGUZGAMBO,[32] NAGHMEH RADHAKRISHNA,[6] HELEN REDDEL,[31] JANET RIMMER,[5,38] ANNE MARIE SOUTHCOTT,[22] MICHAEL SUTHERLAND,[39] FRANCIS THIEN,[40] PETER A.B. WARK,[1,3] IAN A. YANG,[41,42] ELAINE YAP[20] AND PETER G. GIBSON[1,3]

[1]*Centre of Excellence in Severe Asthma and Priority Research Centre for Healthy Lungs, Faculty of Health, University of Newcastle, Callaghan, NSW, Australia;* [2]*Institut universitaire de cardiologie et de pneumologie de Québec, Université Laval, Québec, QC, Canada;* [3]*Department of Respiratory and Sleep Medicine, John Hunter Hospital, New Lambton Heights, NSW, Australia;* [4]*South Western Sydney Clinical School, UNSW Sydney, Liverpool, NSW, Australia;* [5]*Woolcock Institute of Medical Research, The University of Sydney, Glebe, NSW, Australia;* [6]*Difficult Asthma Clinic, Allergy, Asthma and Clinical Immunology, Alfred Health, Melbourne, VIC, Australia;* [7]*Department of Thoracic Medicine, Concord Hospital, Concord, NSW, Australia;* [8]*Lung and Sleep Medicine, Monash University and Medical Centre, Clayton, VIC, Australia;* [9]*Department of Lung Research, Hanson Institute, Adelaide, SA, Australia;* [10]*Department of Thoracic Medicine, Royal Adelaide Hospital, Adelaide, SA, Australia;* [11]*The University of Queensland Diamantina Institute, Woolloongabba, QLD, Australia;* [12]*Department of Respiratory Medicine, Princess Alexandra Hospital, Woolloongabba, QLD, Australia;* [13]*Department of Respiratory Medicine, Liverpool Hospital and School of Medicine, UNSW Sydney, Liverpool, NSW, Australia;* [14]*Respiratory Department, Waikato Hospital, Hamilton, New Zealand;* [15]*Department of Respiratory, Allergy and Sleep Medicine, Flinders Medical Centre, Bedford Park, SA, Australia;* [16]*Department of Medicine, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand;* [17]*Department of Respiratory Medicine, Fiona Stanley Hospital, Murdoch, WA, Australia;* [18]*Department of Respiratory and Sleep Medicine, Campbelltown Hospital, Campbelltown, NSW, Australia;* [19]*School of Medicine, Western Sydney University, Campbelltown, NSW, Australia;* [20]*Respiratory Department, Middlemore Hospital, Auckland, New Zealand;* [21]*Department of Medicine, Melbourne Clinical School, University of Melbourne, Melbourne, VIC, Australia;* [22]*Department of Respiratory and Sleep Disorders Medicine, Western Health, Footscray, VIC, Australia;* [23]*Concord Clinical School and Respiratory Discipline, University of Sydney, Concord, NSW, Australia;* [24]*Respiratory Group, The George Institute for Global Health, Newtown, NSW, Australia;* [25]*Respiratory Medicine, UNSW Sydney, Liverpool, NSW, Australia;* [26]*Immunology Department, Campbelltown Hospital, Campbelltown, NSW, Australia;* [27]*St George Specialist Centre, Kogarah, NSW, Australia;* [28]*Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Singapore;* [29]*Duke - National University Singapore Medical School, Singapore;* [30]*Woolcock Institute of Medical Research, Quality Use of Respiratory Medicines, The University of Sydney, Glebe, NSW, Australia;* [31]*Department of Respiratory Medicine, Royal Prince Alfred Hospital, Camperdown, NSW, Australia;* [32]*Respiratory Services, MidCentral Health, Palmerston North Hospital, Palmerston North, New Zealand;* [33]*Faculty of Medicine, Nursing and Health Sciences, Monash University, Clayton, VIC, Australia;* [34]*Department of Thoracic Medicine, Frankston Hospital, Frankston, VIC, Australia;* [35]*Sydney Medical School, University of Sydney, Camperdown, NSW, Australia;* [36]*Ludwig Engel Centre for Respiratory Research, Westmead Institute of Medical Research, Westmead, NSW, Australia;* [37]*Department of Respiratory and Sleep Medicine, Westmead Hospital, Westmead, NSW, Australia;* [38]*Thoracic Medicine, St Vincent's Clinic, Darlinghurst, NSW, Australia;* [39]*Department of Respiratory and Sleep Medicine, Austin Hospital, Heidelberg, VIC, Australia;* [40]*Department of Respiratory Medicine, Eastern Health and Monash University, Box Hill, VIC, Australia;* [41]*The Prince Charles Hospital, Metro North Hospital and Health Service, Chermside West, QLD, Australia;* [42]*UQ Thoracic Research Centre, Faculty of Medicine, The University of Queensland, Chermside, QLD, Australia*

Correspondence: Vanessa M. McDonald, Centre of Excellence in Severe Asthma and Priority Research Centre for Healthy Lungs, Hunter Medical Research Institute, Faculty of Health and Medicine, University of Newcastle, 1 Kookaburra Circuit, New Lambton Heights, NSW 2305, Australia. Email: vanessa.mcdonald@newcastle.edu.au

Received 27 April 2018; invited to revise 2 June 2018; revised 18 July 2018; accepted 31 July 2018 (Associate Editor: Chi Chiu Leung; Senior and Handling Editor: Lutz Beckert).

ABSTRACT

Background and objective: **A new taxonomic and management approach, termed treatable traits, has been proposed for airway diseases including severe asthma. This study examined whether treatable traits could be identified using registry data and whether particular treatable traits were associated with future exacerbation risk.**

© 2018 Asian Pacific Society of Respirology

Methods: **The Australasian Severe Asthma Web-Based Database (SAWD) enrolled 434 participants with severe asthma and a comparison group of 102 participants with non-severe asthma. Published treatable traits were mapped to registry data fields and their prevalence was described. Participants were characterized at baseline and every 6 months for 24 months.**
Results: **In SAWD, 24 treatable traits were identified in three domains: pulmonary, extrapulmonary and behavioural/risk factors. Patients with severe asthma expressed more pulmonary and extrapulmonary treatable traits than non-severe asthma. Allergic sensitization, upper-airway disease, airflow limitation, eosinophilic inflammation and frequent exacerbations were common in severe asthma. Ten traits predicted exacerbation risk; among the strongest were being prone to exacerbations, depression, inhaler device polypharmacy, vocal cord dysfunction and obstructive sleep apnoea.**
Conclusion: **Treatable traits can be assessed using a severe asthma registry. In severe asthma, patients express more treatable traits than non-severe asthma. Traits may be associated with future asthma exacerbation risk demonstrating the clinical utility of assessing treatable traits.**

Key words: co-morbidity, exacerbation, registry, severe asthma, treatable traits.

SUMMARY AT A GLANCE

We assessed the prevalence of treatable traits in severe asthma compared with non-severe asthma, and assessed the relationship between treatable traits and future exacerbation risk. We demonstrate the usefulness of the treatable traits approach in severe asthma and which specific treatable traits are predictive of future asthma attacks.

Abbreviations: ACQ6, Asthma Control Questionnaire, 6-item; AFL, airflow limitation; AQLQ, Asthma Quality of Life Questionnaire; BMA, Bayesian Model Averaging; CI, confidence interval; CO, carbon monoxide; CT, computed tomography; CVD, cardiovascular disease; DAG, directed acyclic graph; FBC, full blood count; FeNO, exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GORD, gastro-oesophageal reflux disease; HADS, Hospital Anxiety and Depression Scale; ICS, inhaled corticosteroid; IQR, interquartile range; IRR, incidence rate ratio; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; OSA, obstructive sleep apnoea; SAWD, Severe Asthma Web-Based Database; SPT, skin-prick test; VCD, vocal cord dysfunction; WAP, written action plan.

INTRODUCTION

Severe asthma is a heterogeneous disease of the airways that is complicated by frequent attacks and co-morbidities. A 2017 Lancet commission proposed that the current concept of airway diseases fails to recognize the complexity of disease and does little to promote individualized management.[1] To address this issue, a new approach has been proposed that characterizes individuals with airway diseases by the presence of potentially modifiable elements that impact symptoms and prognosis, called treatable traits.[2–4] Management is subsequently individually tailored to directly target these identified traits. A treatable trait is defined as a phenotypic or endotypic characteristic that can be successfully targeted with treatment.[3] In COPD[5] and in older patients with airway diseases,[6] this approach shows great promise; however, its usefulness in severe asthma has not been established.

Furthermore, while the method of assessing treatable traits has been described[1–3] and applied in ambulatory research clinics,[5,6] the assessment of treatable traits in other clinically relevant settings is unknown. Severe asthma registries are used to describe disease characteristics and treatment responses in a real-life clinic setting and therefore represent an emerging data source that complements efficacy data. It is not known whether severe asthma registries can be used to identify treatable traits in severe asthma, nor whether these traits are able to predict future risk of asthma attacks.

Our first aim was to determine whether the identification of treatable traits is possible using a severe asthma registry. Second, we aimed to assess the prevalence of treatable traits in severe asthma compared with non-severe asthma, and to assess the relationship between treatable traits and future exacerbation risk. We hypothesized that treatable traits could be recognized using severe asthma registry data and that they would predict future asthma exacerbation risk.

METHODS

The Severe Asthma Web-Based Database (SAWD) is a multicentre study across 26 sites in Australia, New Zealand and Singapore launched by the Australasian Severe Asthma Network under the governance of the Thoracic Society of Australia and New Zealand. SAWD comprises a cross-sectional evaluation of patient characteristics and a 2-year prospective cohort study.

Included in the registry were adults with severe asthma, confirmed by variable airflow limitation (AFL) within the last 10 years and poor control[7] despite high-dose inhaled corticosteroids (ICS) and a second controller (Appendix S1, Supplementary Information). Inhalation technique, education, adherence and written action plan (WAP) had to be optimized prior to inclusion. A group with non-severe asthma with proven variable AFL, controlled stable disease and maintenance ICS therapy were included as a comparison group. Participants with non-severe asthma were recruited via approved research databases and investigators' clinical practices. A primary diagnosis of lung disease other than asthma, cognitive impairment, current malignancy, an inability to attend visits and pregnancy were exclusions.

Ethical approval was obtained from relevant human research ethics committees or institutional review boards, according to country-specific requirements (lead HNEHREC 12/11/21/4.04). All participants provided written, informed consent.

© 2018 Asian Pacific Society of Respirology

Registry assessments

Demographic characteristics, medication use, asthma and co-morbidity history, asthma control (Asthma Control Questionnaire, 6-item, ACQ6[8]), asthma quality of life (Asthma Quality of Life Questionnaire, AQLQ[9]) and anxiety and depression (Hospital Anxiety and Depression Scale; HADS[10]) were assessed at baseline. Participants underwent spirometry, allergen skin-prick tests and blood tests (full-blood count, total and specific IgE). Exhaled nitric oxide and induced sputum were optional. Past-year exacerbations were identified using a standardized assessment as defined previously.[11] Additional clinical investigations performed within the last 5 years were logged in the database, including polysomnography, 24-h oesophageal pH monitoring, computed tomography (CT) of the chest, sinus CT, oesophagoscopy and laryngoscopy.

Database analysis

Cross-sectional baseline data were used to determine the prevalence of treatable traits. Treatable traits were risk factors and management issues associated with asthma that were identifiable and could be targeted for management. We conducted a mapping exercise where traits proposed by Gibson *et al.*[2] and Agusti *et al.*[3] were compared with data fields from SAWD. If <10% of the sample had a valid assessment for a trait, it was excluded from analysis.

Statistical analysis

Descriptive statistics were computed and differences between severe and non-severe asthma compared using Fisher's exact test, Student's t-test or Wilcoxon rank sum test, as appropriate. To account for the varying total number of traits reported in each individual, the number of treatable traits identified was expressed as the proportion of identified traits over the number of traits assessed. Spearman's correlations were performed to examine the intercorrelation between multiple traits (Table S1, Supplementary Information).

Treatable traits were entered into separate negative binomial regression analyses to predict the number of exacerbations during follow-up, offset by duration of follow-up data available and clustering standard errors by study site. A secondary, multivariable analysis was conducted to adjust for confounding. Covariates were selected for inclusion using a causal diagram (directed acyclic graph (DAG); Appendix S1, Fig. S1 (Supplementary Information)). The DAG was created using known evidence-based causal/association pathways.

To examine how multiple treatable traits predict exacerbations over time, that is by including all traits, negative binomial Bayesian Model Averaging (BMA) was conducted[12] (Appendix S1, Supplementary Information). From the analysis, we reported the best 154 models of the data, illustrated in a heat-map, to demonstrate the proportion of models in which each predictor was included, known as the posterior inclusion probability.

BMA was conducted in the R programming environment (R Foundation, Vienna, Austria) using the bic.glm command of the BMA package,[13] with Occam's window algorithm and a uniform prior distribution. Other analyses were conducted in Stata IC/15 (StataCorp LLC, College Station, TX, USA). The significance level for frequentist analyses was set at 0.05.

RESULTS

Baseline characteristics

There were 434 individuals with severe and 102 individuals with non-severe asthma who completed the cross-sectional assessment between July 2013 and April 2017. Groups were similar demographically, with a predominance of women (Table 1).

Treatable traits identification

The prevalence of 24 treatable traits could be assessed using information contained in the database; 18 identified by Agusti *et al.*[3] and additional traits identified by Gibson *et al.*[2] The assessments and definitions used for identification are shown in Table 2.[2,6] As asthma management skills were optimized in the severe asthma group prior to registry entry, these traits were excluded from analysis. Bacterial colonization was also excluded due to insufficient data. The treatable traits domains are pulmonary (7 traits), extrapulmonary (13 traits) and behavioural/risk factors (4 traits). The traits were independently coded in a subset of 343 SAWD participants by two authors (K.G., S.A.H.). Inter-rater reliability was very high for most traits (agreement: 90–100%; kappa: 0.80–1.00) and satisfactory for upper airway disease (kappa $\pm$ SE: 0.71 ± 0.05), cardiovascular disease (CVD) (0.74 ± 0.05) and inhaler device polypharmacy (0.51 ± 0.05) (Table S2, Supplementary Information).

Treatable traits prevalence

The median (interquartile range, IQR) number of traits assessed out of a possible 24 was 22 (20–23) in the severe group and 22.5 (21–23) in the non-severe group.

Participants with severe asthma expressed a median of 29% (IQR: 22–37%) of the possible traits assessed and non-severe asthma expressed 19% (IQR: 14–27%, $P < 0.001$) (Fig. 1A). Individuals with severe asthma had more pulmonary (33%, IQR: 17–50%) and extrapulmonary traits (25%, IQR: 15–38%) compared with non-severe asthma (17%, IQR: 0–33%, $P < 0.001$; 15%, IQR: 8–27%, $P < 0.001$, respectively). The proportion of traits expressed in the behavioural/risk factor domain was similar between groups (both were 25%).

The prevalence of the individual traits is shown in Table 2 and Figure 1B–D. The following traits were significantly more prevalent in severe asthma than non-severe: incompletely reversible AFL, being prone to exacerbation, neutrophilic airway inflammation, obesity, vocal cord dysfunction (VCD), obstructive sleep apnoea (OSA), depression, systemic inflammation, gastro-oesophageal reflux disease (GORD), inhaler device polypharmacy and Aspergillus sensitization (Table 2).

Treatable traits and exacerbation risk

The severe asthma group reported more baseline past-year exacerbations ($P < 0.001$), irrespective of exacerbation

 © 2018 Asian Pacific Society of Respirology

Table 1 Baseline characteristics by asthma severity status

Characteristics	Severe asthma (n = 434)	Non-severe asthma (n = 102)	P
Female, *n* (%)	260 (59.9)	56 (54.9)	0.372
Age, mean (SD)	54.8 (14.9)	56.0 (16.9)	0.506
Asthma duration, mean (SD)	30.7 (19.0)	32.4 (19.4)	0.419
Smoking status, *n* (%)			
Never smoked	267 (62.2)	66 (66.0)	0.223
Ex-smoker	149 (34.7)	34 (34.0)	
Current smoker	13 (3.0)	0 (0)	
Pack years, median (IQR)	10.5 (2.4, 26.8)	5.9 (1.0, 13.8)	0.018
ICS daily dose μg, beclomethasone equivalent units, median (IQR)	2000.0 (1600.0, 2000.0)	720.0 (400.0, 800.0)	<0.001
Additional medications, *n* (%)			
LABA	423 (97.5)	92 (90.2)	0.002
OCS	106 (24.4)	0 (0)	<0.001
LTRA	64 (14.8)	6 (5.9)	0.014
LAMA	180 (41.5)	11 (10.8)	<0.001
Theophylline	29 (6.7)	3 (2.9)	0.242
Anti-IgE (omalizumab)	83 (19.1)	0 (0)	<0.001
Number of respiratory medications, median (IQR)	4.0 (3.0, 5.0)	2.0 (2.0, 3.0)	<0.001
Pre-bronchodilator FEV_1, % predicted, mean (SD)	66.9 (21.2)	79.7 (19.4)	<0.001
Pre-bronchodilator FEV_1/FVC, mean (SD)	0.8 (0.2)	0.9 (0.1)	<0.001
Post-bronchodilator FEV1, % predicted, mean (SD)	73.1 (21.9)	83.5 (19.3)	<0.001
Post-bronchodilator FEV_1/FVC, mean (SD)	0.8 (0.2)	0.9 (0.1)	<0.001
ACQ6, median (IQR)	2.0 (1.2, 2.8)	0.7 (0.3, 1.0)	<0.001
AQLQ, median (IQR)	5.0 (3.8, 5.8)	6.2 (5.7, 6.6)	<0.001
Past year exacerbations			
Number of OCS courses, median (IQR)	2 (0, 4)	0 (0, 1)	<0.001
Ever visited emergency room, *n* (%)	104 (24.0)	4 (3.9)	<0.001
Ever hospitalized, *n* (%)	96 (22.1)	2 (2.0)	<0.001

Percentages calculated on non-missing data.

ACQ6, Asthma Control Questionnaire, 6-item; AQLQ, Asthma Quality of Life Questionnaire; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid.

type (Table S3, Supplementary Information). During prospective follow-up, participants with severe asthma also reported more exacerbations (median (IQR): 2 (0, 4.1)) compared to those with non-severe asthma (0 (0, 2.0), $P < 0.001$). Sensitivity analyses excluding participants on omalizumab or mepolizumab at any assessment (n = 108) did not change exacerbation findings.

To identify treatable traits predictive of future exacerbation risk we created a DAG, which was informed by current knowledge of possible causal and therefore potentially treatable risk factors (Fig. S1, Supplementary Information). These associations were tested in regression models, and each of the traits were measured as the ratio of the rate of exacerbations in the trait-positive group to the rate in the trait-negative group, and summarized as the incidence rate ratio (IRR). For each additional trait present, there was a 13% increase in exacerbation risk ($P < 0.001$; Table 3). The magnitude of risk was similar within the pulmonary and extrapulmonary domains (IRR: 1.16, $P = 0.018$; IRR: 1.15, $P < 0.001$, respectively). Of the pulmonary traits, eosinophilic inflammation and being prone to exacerbation were associated with future exacerbation risk. The extrapulmonary traits of upper airway disease, VCD, OSA, depression, anxiety, underweight and systemic inflammation were associated with increased exacerbation risk, as was inhaler device polypharmacy. Figure 2 illustrates the modified DAG, presenting only those traits that significantly increased exacerbation risk over time. Similarly, sensitivity analysis representing trait severity largely did not change the results (Table S4, Supplementary Information).

In evaluating predictors of future exacerbations, we also considered all treatable traits together in a BMA analysis. Being prone to exacerbations prior to study entry, number of follow-up visits completed, inhaler device polypharmacy, OSA, age and depression emerged as the best predictors of exacerbation risk in patients with severe asthma (Fig. 3, Table S5 (Supplementary Information).

DISCUSSION

Using a severe asthma registry database, we identified the prevalence of 24 treatable traits. Many pulmonary

© 2018 Asian Pacific Society of Respirology

Table 2 Treatable traits assessment and prevalence

Treatable traits	Assessment tool	Guide for identification	Severe asthma		Non-severe asthma		
			Expressed/ Assessed (*n*)	%	Expressed/ Assessed (*n*)	%	*P*
Pulmonary traits							
Incompletely reversible AFL	Spirometry	Post-bronchodilator $FEV_1/FVC < 0.7$	183/314	58.3	34/87	39.1	0.002
Airflow variability[†]	Spirometry	$FEV_1 \geq 200$ mL and ≥12% post-bronchodilator	63/255	24.7	15/83	18.1	0.233
Eosinophilic inflammation	Induced sputum FeNO FBC	Sputum eosinophils ≥3% and/or FeNO ≥30 ppb and/or blood eosinophils $\geq 0.3 \times 10^9$/L	210/397	52.9	54/90	60.0	0.242
Neutrophilic inflammation[‡]	Induced sputum	Sputum neutrophils ≥61%	20/86	23.3	1/27	3.7	0.023
Bronchiectasis	Self-report Chest CT	Doctor and/or radiologist diagnosis	30/434	6.9	3/102	2.9	0.171
Emphysema	Self-report Chest CT	Doctor and/or radiologist diagnosis	7/434	1.6	1/102	1.0	1.000
Exacerbation prone[‡]	Self-report	≥2 Courses of systemic corticosteroids in the last 12 months	223/434	51.4	6/102	5.9	<0.001
Extrapulmonary traits							
Upper airway disease[§]	Self-report Sinus CT	Doctor or radiologist diagnosis	285/434	65.7	59/102	57.8	0.168
GORD	Self-report	Doctor or radiologist diagnosis	213/434	49.1	37/102	36.3	0.021
VCD	Self-report Larynx CT	Doctor or radiologist diagnosis	29/434	6.7	1/102	1.0	0.028
Dysfunctional breathing	Self-report	Reported	15/434	3.5	1/102	1.0	0.329
OSA	Self-report PSG	Reported	75/434	17.3	7/102	6.9	0.009
Cardiovascular disease[††]	Self-report	Reported	140/434	32.3	39/102	38.2	0.294
Osteoporosis[‡]	Self-report Bone density	Reported	62/434	14.3	8/102	7.8	0.102
Depression	HADS	Depression domain score ≥ 8	104/418	24.9	9/99	9.1	<0.001
Anxiety	HADS	Anxiety domain score ≥ 8	157/418	37.6	30/99	30.3	0.201
Obesity	BMI	BMI ≥ 30 kg/m^2	213/431	49.4	27/102	26.5	<0.001
Underweight[‡]	BMI	BMI < 18.5 kg/m^2	2/431	0.5	1/102	1.0	0.472
Systemic inflammation	FBC	Leukocyte count $>9 \times 10^9$/L	159/388	41.0	11/84	13.1	<0.001
Anaemia[‡]	FBC	Hb < 140 g/L in men and < 120 g/L in women	57/363	15.7	15/81	18.5	0.509
Behavioural traits/risk factors							
Inhaler device polypharmacy[¶]	Medication review	Prescription of three or more different inhalers	126/431	29.2	18/102	17.6	0.018
Smoking	Self-report Exhaled CO	Report current smoking and/or exhaled CO ≥ 10 ppm	20/429	4.7	1/100	1.0	0.149

© 2018 Asian Pacific Society of Respirology

Table 2 Continued

Treatable traits	Assessment tool	Guide for identification	Severe asthma		Non-severe asthma		
			Expressed/ Assessed (*n*)	%	Expressed/ Assessed (*n*)	%	*P*
Allergic sensitization	Specific IgE SPT	At least one positive allergen on immunocap for specific IgE or SPT	214/269	79.6	67/82	81.7	0.753
Aspergillus sensitization‡	Specific IgE SPT	Immunocap or SPT positive to aspergillus extract	117/302	38.7	16/83	19.3	0.001

Percentages calculated on non-missing data.
†Demonstrable within 7 days of first assessment.
‡Identified by Gibson *et al.*[2] only, with remainder identified by Agusti *et al.*[3] or both.
¶Based on use of the following inhaler types: pressurized metred device inhaler, Turbuhaler (AstraZeneca), Accuhaler (GlaxoSmithKline), Autohaler (iNova), Aerolizer (Merck), Handihaler (Boehringer Ingelheim), Breezhaler (Novartis), Respimat (Boehringer Ingelheim), Ellipta (GlaxoSmithKline), Genuair (Menarini) and nasal steroid inhaler.
§Allergic rhinitis, nasal polyps and sinusitis.
††Includes hypertension.
AFL, airflow limitation; BMI, body mass index; CO, carbon monoxide; CT, computed tomography; FBC, full blood count; FeNO, exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GORD, gastro-oesophageal reflux disease; HADS, Hospital Anxiety and Depression Scale; Hb, haemoglobin; IgE, immunoglobuin E; OSA, obstructive sleep apnoea; ppb, parts per billion; ppm, parts per million; PSG, polysomnography; SPT, skin-prick test; VCD, vocal cord dysfunction.

and extrapulmonary traits were significantly more prevalent in severe asthma, demonstrating the additional burden experienced by this group. Importantly, we also identified the treatable traits that predicted increased future exacerbation risk, highlighting the clinical utility of this approach.

We defined treatable traits as relevant characteristics of airway diseases that can be targeted for individualized management. This definition is consistent with the concepts described by Agusti *et al.*[3] and in our prior work.[6] Of the 24 traits identified in the registry, five were not included in Agusti *et al.*'s proposal: prone to exacerbation, neutrophilic inflammation, Aspergillus sensitization, osteoporosis and anaemia. They were however found in other related management approaches[2,6,14,15] and fulfilled our definition of treatable traits. If this new taxonomic system is to be adopted, we will need to reach a consensus on which treatable traits, identified thus far, are important in airway disease management. Data from this study can be used to inform this discussion.

This study reports the prevalence of treatable traits using a severe asthma registry, and importantly, describes the usefulness of this approach in severe asthma. Cross-sectional characterization studies of other severe asthma cohorts have been previously published,[16–21] but reporting of co-morbidities was limited in most. Some other studies of systematic assessments in severe asthma were more comprehensive.[22–25] In agreement with these, we found that a substantial proportion of patients presented with allergic sensitization, upper airway disease, eosinophilic inflammation, obesity, GORD, psychological issues and repeated exacerbations.[16–20,23,25]

The number of identified traits in the behavioural/risk factors domain were not more prevalent in severe asthma, and an increasing number of traits in this domain did not increase exacerbation risk. However, these data should be interpreted with caution, as traits that are known to be associated with poorer outcome, such as inadequate inhaler technique, non-adherence and lack of a WAP, were not included in these analyses, since these skills were optimized before study entry. Other behavioural traits may not be readily reported by patients.

Exacerbations of severe asthma are common and have negative impacts on health outcomes.[26] Exacerbation avoidance is key to management, with the Lancet commissioners for *Redefining Airways Disease* calling for zero tolerance on attacks.[1] We found that during prospective follow-up, the median rate of attacks was two/person/year, and in severe asthma the exacerbation rate was 2.36 times that of non-severe asthma. We sought to determine treatable trait predictors for future exacerbations, in order to inform key targets for future research. We did this in two ways, first we considered traits that were known to be associated or have a causal relationship with attacks. We tested the associations in regression models; in some cases, the trait had a direct link to exacerbations and, in others, it was via a linked pathway to exacerbations (Fig. S1, Supplementary Information). This novel analysis identified traits associated with increased exacerbation risk including VCD, raising

© 2018 Asian Pacific Society of Respirology

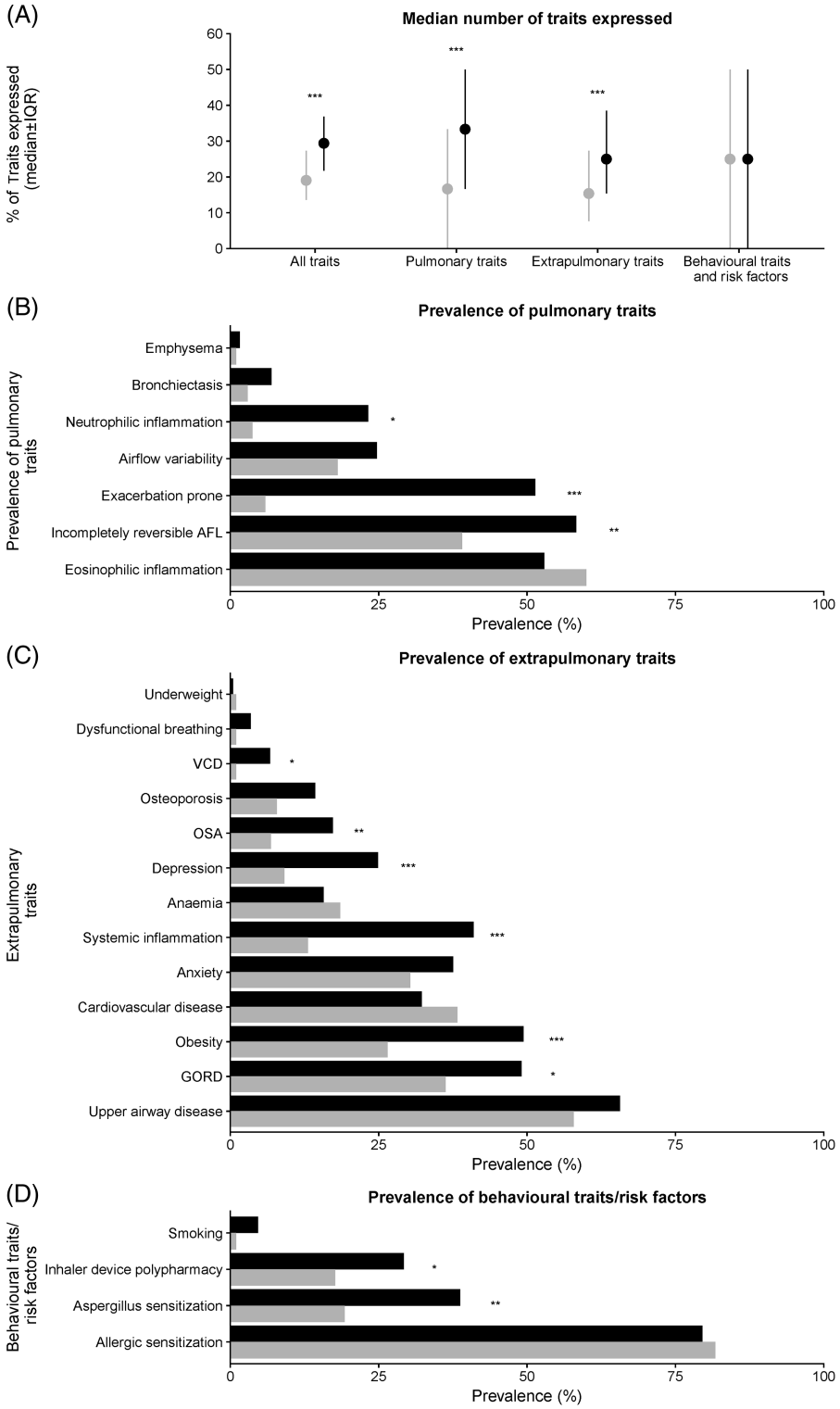


Figure 1 Treatable traits in severe and non-severe asthma. (A) Median proportion of treatable traits present (± interquartile range) in the non-severe asthma (●) and severe asthma (●) groups. Prevalence of treatable traits, separated as (B) pulmonary traits, (C) extrapulmonary traits and (D) behavioural traits and risk factors (■, non-severe asthma; ■, severe asthma). **P* < 0.05; ***P* < 0.01; ****P* < 0.001. GORD, gastro-oesophageal reflux disease; OSA, obstructive sleep apnoea; VCD, vocal cord dysfunction.

the question of whether some of these exacerbations were actually VCD episodes. Anxiety, depression, upper airway disease, OSA and eosinophilic inflammation were also associated with exacerbation risk, as has been previously reported in severe asthma and/or COPD.[27,28] Interestingly, inhaler device polypharmacy and being underweight emerged as predictors despite no direct or indirect link proposed in the DAG. These results highlight important traits that could be targeted in an effort to reduce attacks, informing future clinical trials.

Our second approach for examining exacerbation predictors was the use of BMA. The best of all models involved the predictors of being prone to exacerbation, number of visits completed, inhaler device polypharmacy and OSA. Being exacerbation prone at baseline and

© 2018 Asian Pacific Society of Respirology

© 2018 Asian Pacific Society of Respirology

Table 3 Predicting exacerbations over follow-up (6–24 months) in severe and non-severe asthma

Asthma characteristics and treatable traits	Unadjusted IRR	95% CI	*P*	Adjusted IRR	95% CI	*P*	Covariates in adjusted analyses[†]
Asthma characteristics							
Severe asthma (reference: non-severe asthma)	2.36	1.93, 2.90	<0.001				
ACQ6	1.46	1.34, 1.59	<0.001				
All treatable traits							
Total number of traits present	1.13	1.06, 1.20	<0.001				
Pulmonary traits							
Incompletely reversible AFL	0.93	0.67, 1.28	0.646	0.71	0.37, 1.37	0.309	Age, bronchiectasis, emphysema, neutrophilic inflammation
Airflow variability	1.31	0.80, 2.15	0.279	1.37	0.82, 2.27	0.225	Eosinophilic inflammation
Eosinophilic inflammation	0.98	0.66, 1.47	0.929	1.35	1.10, 1.65	0.005	Allergic sensitization
Neutrophilic inflammation	1.10	0.96, 1.26	0.169	1.12	0.95, 1.32	0.161	Age, bronchiectasis, smoking, systemic inflammation
Bronchiectasis	1.21	0.91, 1.60	0.186	1.17	0.87, 1.58	0.290	GORD
Emphysema	0.94	0.53, 1.66	0.833	1.07	0.63, 1.82	0.802	Age, smoking
Exacerbation prone	2.07	1.66, 2.58	<0.001	2.07	1.66, 2.58	<0.001	None
Total number of pulmonary traits present	1.16	1.03, 1.32	0.018				
Extrapulmonary traits							
Upper airway disease	1.11	0.89, 1.38	0.342	1.26	1.03, 1.55	0.024	Allergic sensitization, Eosinophilic inflammation.
GORD	1.24	0.84, 1.84	0.282	1.23	0.81, 1.87	0.328	Obesity
VCD	1.62	1.21, 2.17	0.001	1.51	1.22, 1.88	<0.001	Anxiety, GORD, upper airway disease
Dysfunctional breathing	1.61	0.85, 3.03	0.141	1.68	0.75, 3.74	0.206	Anxiety, VCD
OSA	1.40	1.03, 1.92	0.033	1.41	1.05, 1.89	0.022	Obesity, upper airway disease
Cardiovascular disease	0.91	0.72, 1.15	0.413	0.91	0.72, 1.15	0.432	Smoking
Osteoporosis	1.41	0.90, 2.21	0.137	1.41	0.90, 2.21	0.137	None
Depression	1.64	1.43, 1.89	<0.001	1.63	1.41, 1.88	<0.001	Gender, obesity
Anxiety	1.31	1.06, 1.61	0.013	1.27	1.03, 1.56	0.023	Gender
Obesity	1.11	0.86, 1.42	0.424	1.11	0.86, 1.42	0.424	None
Underweight	1.29	1.02, 1.64	0.032	1.29	1.02, 1.64	0.032	None
Systemic inflammation	1.39	1.12, 1.74	0.003	1.40	1.10, 1.79	0.006	Obesity
Anaemia	0.92	0.70, 1.21	0.548	0.92	0.70, 1.21	0.548	None
Total number of extrapulmonary traits present	1.15	1.08, 1.22	<0.001				
Behavioural traits/risk factors							
Inhaler device polypharmacy	1.51	1.31, 1.75	<0.001	1.51	1.31, 1.75	<0.001	None
Smoking	1.69	0.83, 3.47	0.151	1.69	0.83, 3.47	0.151	None
Allergic sensitization	1.03	0.77, 1.38	0.828	1.03	0.77, 1.38	0.828	None
Aspergillus sensitization	1.17	0.92, 1.48	0.206	1.18	0.81, 1.71	0.393	Allergic sensitization
Total number of behavioural traits/risk factors present	1.08	0.91, 1.28	0.382				

[†]Adjustments made according to pathways identified via directed acyclic graph (Fig. S1, Supplementary Information), adjustment for total effect of each predictor on exacerbation outcome.

ACQ6, Asthma Control Questionnaire, 6-item; AFL, airflow limitation; CI, confidence interval; GORD, gastro-oesophageal reflux disease; IRR, incidence rate ratio; OSA, obstructive sleep apnoea; VCD, vocal cord dysfunction.

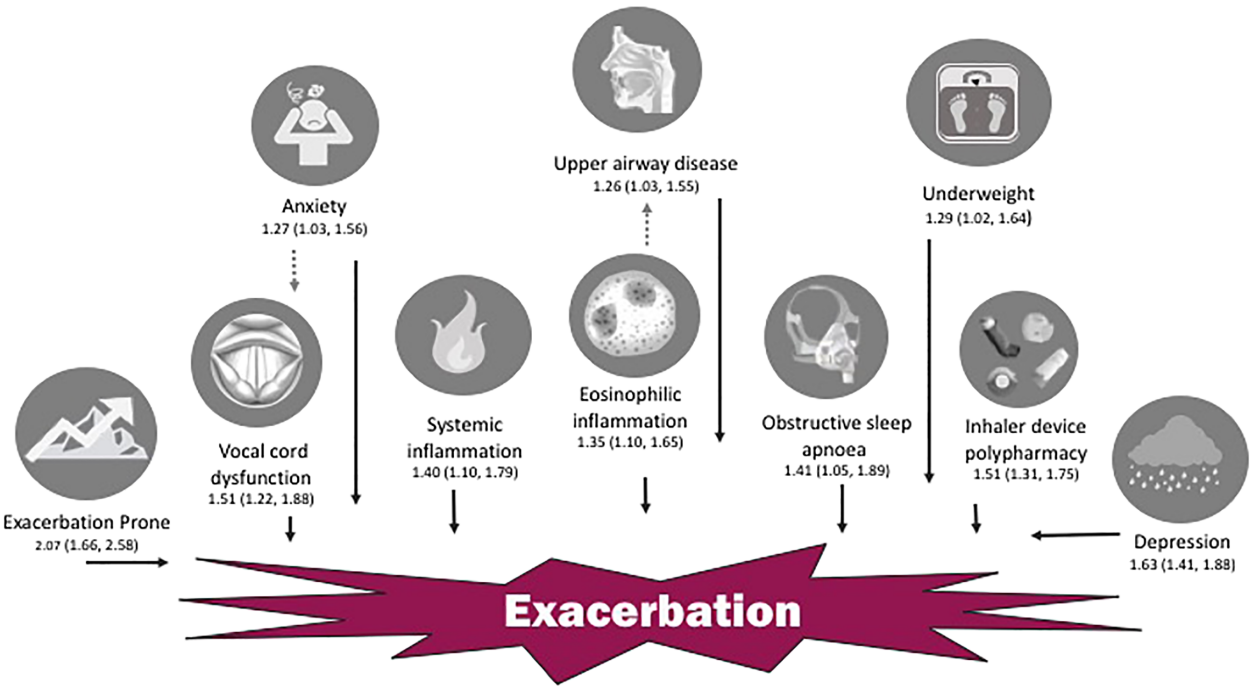


Figure 2 Modified directed acyclic graph depicting treatable traits significantly ($P < 0.05$) associated with increased risk of exacerbations over time. Numbers are the incident rate ratios (IRR) and 95% confidence intervals for the total effect of each trait on exacerbations over time.

number of visits predicts future exacerbation risk in every model. Inhaler device polypharmacy, OSA and depression were also frequently included in the top 154 models, indicating their importance as predictors of exacerbation risk, over and above a history of frequent exacerbations and amount of follow-up time. This is important, as whilst some of these traits may be assessed (e.g. depression) as part of severe asthma systematic assessment, others are not (e.g. OSA and inhaler device polypharmacy), and all are infrequently treated.[21] OSA, inhaler device polypharmacy and depression were significant predictors in both approaches we employed, suggesting concordance of these approaches.

A criticism or counter argument to the treatable trait approach is its complexity and the resources required to implement the range of assessments recommended. Proponents of the approach have suggested that strategies are needed to enable the identification of treatable traits that contribute to poor respiratory health in patients, and be treated accordingly.[29] Our analyses have provided important new knowledge in terms of identifying the treatable traits that matter, at least in terms of exacerbation avoidance. We recognize that the implementation of the treatable traits approach, and the design of randomized controlled trials that aim to test the approach are complex, but necessary. As such, these analyses are important for the progress of research in the area. Identifying the traits that have a large impact informs the design of intervention studies that aim to improve outcomes, including exacerbations. For example, in developing a multicomponent intervention one might start with the traits that predict poor outcome. Another interesting analysis for a prospective treatment study would be to determine if any traits were associated with an improved outcome.

Clinicians and researchers recognize that severe asthma is a heterogeneous disease associated with multiple co-morbidities and behavioural traits, and international guidelines recommend that a systematic assessment is implemented.[7] We previously performed a systematic review and meta-analysis of multidimensional assessment in severe asthma[21] and report that this approach is associated with improvements in health status, asthma control and exacerbations. However, it is also evident that many traits that we have identified as prevalent and associated with future risk are frequently not assessed in severe asthma populations.[21] This present study reports the application of a multidimensional assessment in severe asthma that demonstrates clinical utility and allows the recognition of important traits that predict outcome. It is also clinically feasible, and shows how the use of registry data can be used to inform treatment.

While the registry database provided a large sample size, it had its limitations. The number of traits assessed was limited by the information contained in the database. Hence, some relevant traits could not be evaluated. Most traits were assessed systematically but optional clinical tests that were negative may have been omitted. Physician or self-reported co-morbidities may have underestimated and overestimated prevalence. Like any other registry, missing data was also limiting. In our study, each participant had a median of 2 traits out of 24 missing from the database. To account for the varying number of traits assessed, we reported proportions of identified traits and used this as the basis of our comparisons. Finally, we identified treatable traits based on published recommendations

 © 2018 Asian Pacific Society of Respirology

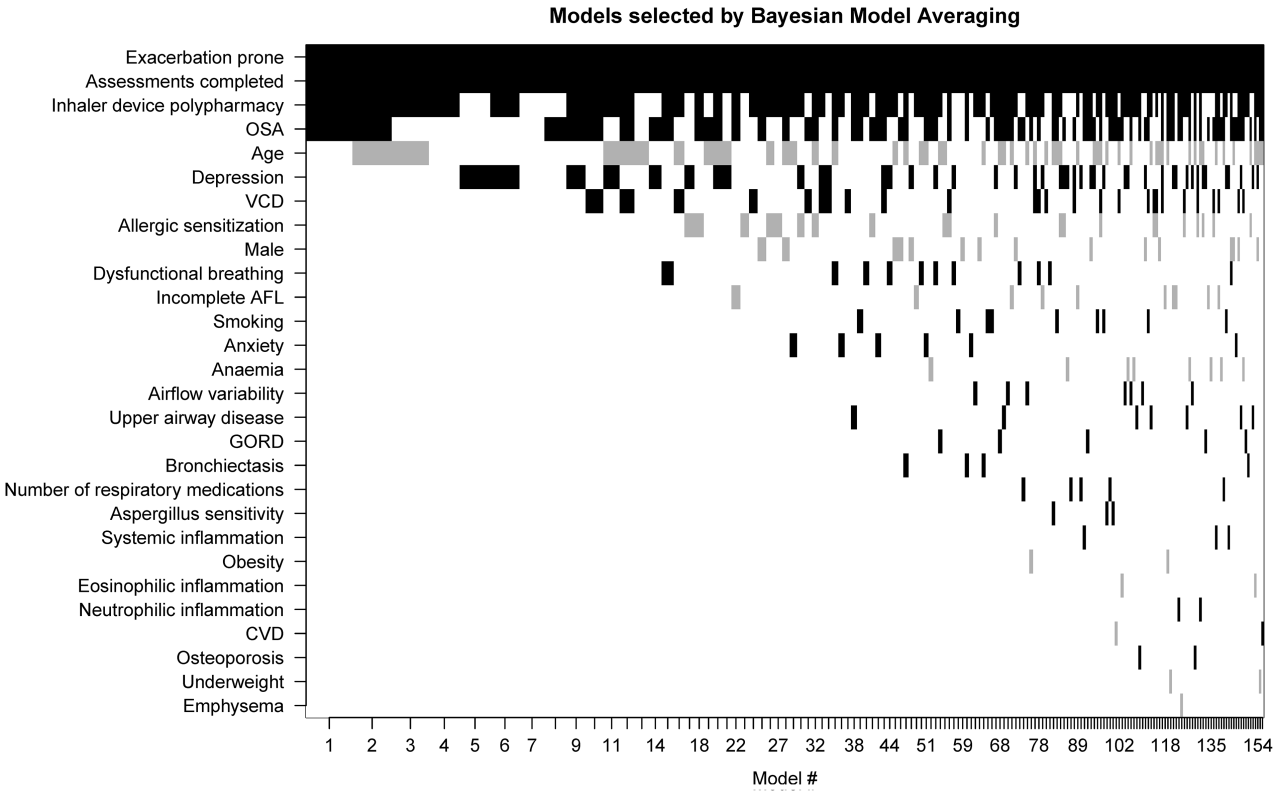


Figure 3 Bayesian Model Averaging heat map demonstrating the top 154 models for predicting exacerbation rate in patients with severe asthma. Predictors are listed on the y-axis in descending order of ability to predict the rate of exacerbation. The models are listed on the x-axis, with the best model for predicting exacerbation risk leftmost; when moving left to right across the figure, each model has less ability to predict exacerbation rate than the model before. Predictors in black are associated with an increased rate of exacerbation and predictors in grey with decreased rate of exacerbation rate. AFL, airflow limitation; CVD, cardiovascular disease; GORD, gastro-oesophageal reflux disease; OSA, obstructive sleep apnoea; VCD, vocal cord dysfunction.

related to this concept.[2,3] Most of these traits are supported by evidence-based treatment recommendations. For some traits, however, such as systematic inflammation and neutrophilic airway inflammation, the evidence to support current treatment strategies is less developed. Similarly, there is also some debate about what is and is not a treatable trait, for example is AFL in severe asthma treatable? We propose that further international consensus is required to determine the accepted treatable traits and their biomarkers.

In conclusion, we have demonstrated that data collected after systematic characterization of asthma patients may be used to identify treatable traits, and we have identified important traits that predict future exacerbation. The results confirm the marked heterogeneity and greater burden associated with severe asthma and reinforce the need for systematic assessment in patients with severe asthma, although the process for translation to clinical practice needs to be defined. Trials evaluating the efficacy and cost-effectiveness of different assessments and interventions are duly needed so that we can define 'treatable traits that matter'.

Acknowledgements

We thank the Thoracic Society of Australia and New Zealand for providing governance and the Woolcock Institute of Medical Research and the Hunter Medical Research Institute. We thank the study participants and members of the Australasian Severe Asthma Network, including SAWD site investigators, clinical research staff, staff involved in data entry staff and personnel involved in statistical and information technology support throughout the project.

Author contribution statement

V.M.M., K.G. and P.G.G. conceived the research question. S.A.H. performed the analysis. V.M.M. and P.G.G. wrote the manuscript. All authors were involved in acquisition of data, interpretation of data, revising the manuscript for intellectual content and approval of the final manuscript for submission.

Disclosure statement

This study was funded through grants from AstraZeneca, GlaxoSmithKline, Novartis, Boehringer Ingelheim and Roche. None of these companies had any involvement in the data analysis or manuscript preparation. Individual author disclosures are presented in Appendix S2 (Supplementary Information). This research was previously presented at the Annual Thoracic Society of Australia and New Zealand (TSANZ) 2018.

REFERENCES

1 Pavord ID, Beasley R, Agustí A, Anderson GP, Bel E, Brusselle G, Cullinan P, Custovic A, Ducharme FM, Fahy JV *et al.* After asthma: redefining airways diseases. *Lancet* 2017; **6736**: 1–51.

© 2018 Asian Pacific Society of Respirology

2 Gibson PG, McDonald VM, Marks GB. Asthma in older adults. *Lancet* 2010; **376**: 803–13.
3 Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, Humbert M, Jones P, Gibson PG, Vestbo J *et al*. Treatable traits: toward precision medicine of chronic airway diseases. *Eur. Respir. J.* 2016; **47**: 410–9.
4 Agusti A, Bafadhel M, Beasley R, Bel EH, Faner R, Gibson PG, Louis R, McDonald VM, Sterk PJ, Thomas M *et al*. Precision medicine in airway diseases: moving to clinical practice. *Eur. Respir. J.* 2017; **50**: pii: 1701655.
5 McDonald V, Higgins I, Wood LG, Gibson PG. Multidimensional assessment and tailored interventions for COPD: respiratory utopia or common sense? *Thorax* 2013; **68**: 691–4.
6 McDonald VM, Simpson JL, Higgins I, Gibson PG. Multidimensional assessment of older people with asthma and COPD: clinical management and health status. *Age Ageing* 2011; **40**: 42–9.
7 Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel EH, Bleecker ER *et al*. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur. Respir. J.* 2014; **43**: 343–73.
8 Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the Asthma Control Questionnaire. *Respir. Med.* 2005; **99**: 553–8.
9 Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. *Chest* 1999; **115**: 1265–70.
10 Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr. Scand.* 1983; **67**: 361–70.
11 Gibson PG, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, Jenkins C, Peters MJ, Marks GB, Baraket M *et al*. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. *Lancet* 2017; **390**: 659–68.
12 Hoeting JA, Madigan D, Raftery AE, Volinsky CT. Bayesian model averaging: a tutorial. *Stat. Sci.* 1999; **14**: 382–401.
13 Raftery A, Hoeting J, Volinsky C, Painter I, Yeung KY. BMA: Bayesian Model Averaging. 2017. [Accessed 24 July 2017.] Available from URL: https://cran.r-project.org/web/packages/BMA
14 Gibson P, McDonald VM. Phenotyping asthma and COPD. *BRN Rev.* 2016; **2**: 239–52.
15 Agusti A, MacNee W. The COPD control panel: towards personalised medicine in COPD. *Thorax* 2013; **68**: 687–90.
16 Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L, Calhoun WJ, Castro M, Chung KF, Clark MP *et al*.; National Heart, Lung, Blood Institute's Severe Asthma Research Program. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J. Allergy Clin. Immunol.* 2007; **119:** 405–13.
17 Shaw DE, Sousa AR, Fowler SJ, Fleming LJ, Roberts G, Corfield J, Pandis I, Bansal AT, Bel EH, Auffray C *et al*.; U-BIOPRED Study Group. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. *Eur. Respir. J.* 2015; **46**: 1308–21.
18 The ENFUMOSA Study Group. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. European Network for Understanding Mechanisms of Severe Asthma. *Eur. Respir. J.* 2003; **22**: 470–7.
19 Heaney LG, Brightling CE, Menzies-Gow A, Stevenson M, Niven RM, British Thoracic Society Difficult Asthma Network. Refractory asthma in the UK: cross-sectional findings from a UK multicentre registry. *Thorax* 2010; **65**: 787–94.
20 Schleich F, Brusselle G, Louis R, Vandenplas O, Michils A, Pilette C, Peche R, Manise M, Joos G. Heterogeneity of phenotypes in severe asthmatics. The Belgian Severe Asthma Registry (BSAR). *Respir. Med.* 2014; **108**: 1723–32.
21 Clark VL, Gibson PG, Genn G, Hiles SA, Pavord ID, McDonald VM. Multidimensional assessment of severe asthma: a systematic review and meta-analysis. *Respirology* 2017; **22**: 1262–75.
22 Heaney LG, Conway E, Kelly C, Johnston BT, English C, Stevenson M, Gamble J. Predictors of therapy resistant asthma: outcome of a systematic evaluation protocol. *Thorax* 2003; **58**: 561–6.
23 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.
24 Robinson DS, Campbell DA, Durham SR, Pfeffer J, Barnes PJ, Chung KF, Asthma and Allergy Research Group of the National Heart and Lung Institute. Systematic assessment of difficult-to-treat asthma. *Eur. Respir. J.* 2003; **22**: 478–83.
25 van der Meer AN, Pasma H, Kempenaar-Okkema W, Pelinck JA, Schutten M, Storm H, Ten Brinke A. A 1-day visit in a severe asthma centre: effect on asthma control, quality of life and healthcare use. *Eur. Respir. J.* 2016; **48**: 726–33.
26 McDonald VM, Gibson PG. Exacerbations of severe asthma. *Clin. Exp. Allergy* 2012; **42**: 670–7.
27 Gibson PG, McDonald VM. Management of severe asthma: targeting the airways, comorbidities and risk factors. *Intern. Med. J.* 2017; **47**: 623–31.
28 Price D, Wilson AM, Chisholm A, Rigazio A, Burden A, Thomas M, King C. Predicting frequent asthma exacerbations using blood eosinophil count and other patient data routinely available in clinical practice. *J. Asthma Allergy* 2016; **9**: 1–12.
29 Fingleton J, Hardy J, Beasley R. Treatable traits of chronic airways disease. *Curr. Opin. Pulm. Med.* 2018; **24**: 24–31.

Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

Appendix S1 Supplementary methods.
Appendix S2 Declaration of interests.
Figure S1 Directed acyclic graph showing relationships between treatable traits in predicting exacerbations.
Table S1 Correlation between traits, with positive correlations denoted in blue and negative correlations in orange.
Table S2 Proportion agreement and kappa interrater reliability of two independent coders of each treatable trait within a subset of SAWD participants.
Table S3 Exacerbations at baseline and across follow-up by severity status.
Table S4 Association between continuous traits at baseline and exacerbations over follow-up.
Table S5 Pooled incident rate ratios and 95% CI and posterior inclusion probability in models (Bayesian Model Averaging).
Visual Abstract Treatable Traits predict future attacks in severe asthma.

© 2018 Asian Pacific Society of Respirology

SUPPLEMENTARY INFORMATION

Treatable traits can be identified in a severe asthma registry and predict future exacerbations

Vanessa M McDonald[1]; Sarah A Hiles[1]; Krystelle Godbout[2]; Erin S Harvey[1,3]; Guy B Marks[4,5]; Mark Hew[6]; Matthew Peters[7]; Philip Bardin[8]; Paul N Reynolds[9]; John W Upham[10]; Melissa Baraket[11]; Zaheerodin Bhikoo[12]; Jeffrey Bowden[13]; Ben Brockway[14]; Li Ping Chung[15]; Belinda Cochrane[16,17]; Gloria Foxley[5]; Jeffrey Garrett[18]; Lata Jayaram[19,20]; Christine Jenkins[7,21,22,23]; Constance Katelaris[17,24]; Gregory Katsoulotos[25]; Mariko S Koh[26,27]; Vicky Kritikos[28,29]; Marina Lambert[30]; David Langton[31,32]; Alexis Lara Rivero[25]; Peter G Middleton[33-35]; Aldoph Nanguzgambo[30]; Naghmeh Radhakrishna[6]; Helen Reddel[29]; Janet Rimmer[5,36]; Anne Marie Southcott[20]; Michael Sutherland[37]; Francis Thien[38]; Peter AB Wark[1,3]; Ian A Yang[39,40]; Elaine Yap[18]; Peter G Gibson[1,3]

1 Centre of Excellence in Severe Asthma and Priority Research Centre for Healthy Lungs, Faculty of Health, University of Newcastle, NSW, Australia.
2 Institut universitaire de cardiologie et de pneumologie de Québec, Université Laval, QC, Canada.
3 Department of Respiratory and Sleep Medicine, John Hunter Hospital, NSW, Australia.
4 South Western Sydney Clinical School, UNSW Sydney, NSW, Australia.
5 Woolcock Institute of Medical Research, The University of Sydney, NSW, Australia.
6 Difficult Asthma Clinic, Allergy, Asthma & Clinical Immunology, Alfred Health, VIC, Australia.
7 Department of Thoracic Medicine, Concord Hospital, NSW, Australia.
8 Lung and Sleep Medicine, Monash University and Medical Centre, VIC, Australia.
9 Lung Research, Hanson Institute and Department of Thoracic Medicine, Royal Adelaide Hospital, SA, Australia.
10 The University of Queensland Diamantina Institute and Department of Respiratory Medicine, Princess Alexandra Hospital, QLD, Australia.
11 Department of Respiratory Medicine, Liverpool Hospital School of Medicine, UNSW Sydney, NSW, Australia.
12 Respiratory Department, Waikato Hospital, Hamilton, New Zealand.
13 Department of Respiratory, Allergy and Sleep Medicine, Flinders Medical Centre, SA, Australia.
14 Department of Medicine, Dunedin School of Medicine, University of Otago, New Zealand.
15 Department of Respiratory Medicine, Fiona Stanley Hospital, WA, Australia.
16 Department of Respiratory and Sleep Medicine, Campbelltown Hospital, NSW, Australia.
17 School of Medicine, Western Sydney University, NSW, Australia.
18 Respiratory Department, Middlemore Hospital, Auckland, New Zealand.
19 Department of Medicine, Melbourne Clinical School, University of Melbourne, VIC, Australia.
20 Department of Respiratory and Sleep Disorders Medicine, Western Health, VIC, Australia.
21 Concord Clinical School and Respiratory Discipline, University of Sydney, NSW, Australia.
22 The George Institute for Global Health, NSW, Australia.
23 Respiratory Medicine, UNSW Sydney, NSW, Australia.
24 Immunology Department, Campbelltown Hospital, NSW, Australia.
25 St George Specialist Centre, NSW, Australia.
26 Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Singapore.
27 Duke - National University Singapore Medical School, Singapore.
28 Woolcock Institute of Medical Research, Quality Use of Respiratory Medicines, The University of Sydney, NSW, Australia.
29 Department of Respiratory Medicine, Royal Prince Alfred Hospital, NSW, Australia.
30 Respiratory Services, MidCentral Health, Palmerston North Hospital, New Zealand.
31 Faculty of Medicine, Nursing and Health Sciences, Monash University, VIC, Australia.
32 Department of Thoracic Medicine, Frankston Hospital, Melbourne, VIC, Australia.
33 Sydney Medical School, University of Sydney, NSW, Australia.
34 Ludwig Engel Centre for Respiratory Research, Westmead Institute of Medical Research, NSW, Australia.
35 Department of Respiratory and Sleep Medicine, Westmead Hospital, NSW, Australia.
36 St Vincent's Clinic, NSW, Australia.

37 Department of Respiratory and Sleep Medicine, Austin Hospital, VIC, Australia.
38 Department of Respiratory Medicine, Eastern Health and Monash University, VIC, Australia.
39 The Prince Charles Hospital, Metro North Hospital and Health Service, QLD, Australia.
40 UQ Thoracic Research Centre, Faculty of Medicine, The University of Queensland, QLD, Australia.

Appendix S1- *Supplementary Methods*

Definition of severe asthma

Severe asthma was defined as the presence of one or more of the following:[1]

- Poor asthma control (6-item Asthma Control Questionnaire (ACQ6) >1.5, Asthma Control Test (ACT) <20 or "not well controlled" according to Global Initiative for Asthma (GINA) or National Education for Education and Prevention Program (NAEPP) guidelines;[2,3]
- ≥2 courses of systemic corticosteroids for asthma in the previous year;
- ≥1 hospitalisation, intensive care admission or mechanical ventilation in the previous year; or
- A pre-bronchodilator forced expiratory volume in 1s (FEV1) <80% in the face of a reduced FEV1/FVC.

According to the definition of severe asthma proposed in the ERS/ATS guidelines[1], contributing factors must be addressed before a definition of severe asthma can be applied. To ensure that the severe asthma participants who were in the registry were truly severe, participants were only included in the registry after an assessment of adherence, self-management and inhaler device technique was performed, and when the treating clinician was satisfied that all attempts had been made to optimise inhaler device technique, asthma management skills and treatment adherence.

Database management and quality control

Data were stored using the Research Electronic Data Capture (REDCap) system.[4] REDCap forms were modified from those initially developed by the Alfred Difficult Asthma Service, Melbourne.[5] Data were anonymised and password-protected. The data custodian and individual sites were responsible for the quality control assessments. Specifically, following patient enrolment, baseline data was reviewed for confirmation of eligibility and classification of asthma severity. Data entry errors and discrepancies were resolved. Selected source data verification (evidence of variable airflow limitation, baseline spirometry and blood results) was also performed. Access to the data was permitted as part of the ethics approved characterisation study and performed in April 2017. Ethical approval was obtained from relevant human research ethics committees or institutional review boards, according to country-specific requirements (Australia: lead HNEHREC 12/11/21/4.04, HREC/13/RAH/379, Alfred Hospital EC 391/13, HREC [Tasmania] Network H0014915, SCGH HREC 2015-133 and Peninsula Health HREC HREC/13/PH/49; New Zealand: HDEC 12/CEN/69; and Singapore: SingHealth CIRB 2016/2550)).

Treatable traits identification

Overall 18 of 24 identified traits in SAWD were proposed in the Agusti *et al.*[6] model, and 15 of the 24 were proposed by Gibson *et al.*[7]. Of the traits identified in SAWD, there was an overlap of 54% between those proposed by Agusti or Gibson, three additional traits proposed by Gibson (neutrophilic inflammation, anaemia and exacerbation prone) were included in the

SAWD analysis, and an additional two (Aspergillus sensitisation and osteoporosis) were included in this analysis but not specifically recommended by either Agusti or Gibson.

The traits were independently coded in a subset of 343 SAWD participants by two authors (KG, SAH). Inter-rater reliability was very high for most traits (agreement 90-100%; kappa 0.80-1.00; Supplementary Table S2), and satisfactory for upper-airway disease (kappa±SE; 0.71± 0.05), cardiovascular disease (CVD) (0.74±0.05) and inhaler-device polypharmacy (0.51±0.05).

Statistics – assumptions in adjusting for confounding

We estimated the effect of each predictor, adjusted for potentially confounding factors, using multivariate regression (negative binomial). We selected the set of covariates for each predictor of exacerbation risk using a causal diagram (directed acyclic graph; DAG; Figure S1) that encodes explicit assumptions underlying the chosen causal model.[8-10] The covariates were chosen if they were known to cause exacerbation or were significantly associated with exacerbations. The DAG was generated based on the expert knowledge of published literature, and four co-authors with extensive expertise in respiratory disease (VMM, MH, GBM and PGG). The initial DAG was created by GBM, VMM then reviewed and included additional covariates, the DAG was then discussed in a team comprising VMM, PGG, MH and SAH and additional edits were made.

Statistics – Bayesian Model Averaging

Bayesian Model Averaging[11] is essentially a Bayesian equivalent of generalized multiple regression, except that instead of estimating a single regression equation with a set number of predictors, millions of regression equations using different combinations of the predictors are estimated simultaneously (in this study with 28 predictors, the number of model tested was 2^{28}, or over 268 million models). Each of the tested models is then weighted by how well it predicts the outcome relative to the other models tested. The output of Bayesian Model Averaging is therefore a weighted average of the set of candidate models that are being considered. In doing so, Bayesian Model Averaging provides an effective approach to dealing with collinearity among predictors and the uncertainty around selecting a single model for the data, which together prevent us from placing too much confidence in any single model (and the predictors included in that model). In the current manuscript, Bayesian Model Averaging was conducted in the R programming environment (R Foundation, Austria) using the bic.glm command of the BMA package,[12] with Occam's window algorithm and a uniform prior distribution.

Results

Where able, we performed additional adjusted analysis to determine whether the severity of the trait impacted the relationship with exacerbation outcome (Supplementary Table S4). For most variables, the conclusions remain the same. When examined as continuous variables the number of exacerbations before baseline, depression score, anxiety score and the number of inhaler devices remained significant predictors.

Underweight (vs. healthy weight; due to reduced power) and white blood cells were no longer significant predictors of exacerbation. All of the eosinophilic airway inflammation indicators are not significant predictors, most likely because we are no longer using a composite measure.

We also saw a new significant association between sputum neutrophils and exacerbation, but the effect is very small (4% increased risk for a 10% increase in neutrophils).

Appendix S2- *Declaration of interests*

VM McDonald is supported by an NHMRC TRIP fellowship and has received speaker fees for unrelated work from AstraZeneca, grants for organising education unrelated to this work from Menarini, and research funds for unrelated work from AstraZeneca, and GlaxoSmithKline. **SA Hiles** was supported by a research grant from GlaxoSmithKline during the conduct of the study. **K Godbout** reports personal fees from AstraZeneca and Boehringer Ingelheim outside the submitted work. **M Hew** reports grants and other support from AstraZeneca, GlaxoSmithKline and Novartis, and other support from Seqirus, outside the submitted work; for all of which his employer Alfred Health has been reimbursed. **M Peters** reports personal fees from GlaxoSmithKline for CME lectures and advisory board participation, personal fees from AstraZeneca, for CME lectures and personal fees from Novartis for advisory board participation outside the submitted work. **PN Reynolds** reports grants from TSANZ during the conduct of the study. **JW Upham** reports personal fees from Novartis, GlaxoSmithKline, AstraZeneca and TEVA outside the submitted work. **J Bowden** reports personal fees from AstraZeneca and GlaxoSmithKline during the conduct of the study. **LP Chung** reports fees for presentation and attendance at board meetings from AstraZeneca, GlaxoSmithKline, Menarini and Boehringer Ingelheim for work unrelated to the current manuscript. **C Jenkins** reports personal fees from Novartis, AstraZeneca and Boehringer Ingelheim, and grants and personal fees from GlaxoSmithKline, outside the submitted work. **V Kritikos** reports other support from AstraZeneca outside the submitted work. **N Radjakrishna** reports personal fees from Mundipharma, AstraZeneca and Boehringer Ingelheim outside the submitted work. **H Reddel** reports grants, personal fees and non-financial support from AstraZeneca, grants, personal fees and non-financial support from GlaxoSmithKline, personal fees from Merck, personal fees from Novartis, personal fees from Teva, personal fees from Mundipharma, personal fees from Boehringer Ingelheim, outside the submitted work. **J Rimmer** reports unrelated honoraria form GlaxoSmithKline, Stallergenes, Seqirus and AstraZeneca. **M Sutherland** reports personal fees from Astra Zeneca outside the submitted work. **PG Gibson** has received research grants and speaker fees from AstraZeneca, GlaxoSmithKline and Novartis. All other co-authors declare no conflict of interest. All other authors have nothing to disclose.

References

1. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel EH, Bleecker ER, Boulet LP, Brightling C, Chanez P, Dahlen SE, Djukanovic R, Frey U, Gaga M, Gibson P, Hamid Q, Jajour NN, Mauad T, Sorkness RL, Teague WG. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43(2):343-73.
2. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention 2014. Available from: http://ginaasthma.org/.

3. National Asthma Education Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol. 2007;120(5 Suppl):S94-138.
4. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81.
5. Tay TR, Lee J, Radhakrishna N, Hore-Lacy F, Stirling R, Hoy R, Dabscheck E, O'Hehir R, Hew M. A structured approach to specialist-referred difficult asthma patients improves control of comorbidities and enhances asthma outcomes. J Allergy Clin Immunol Pract. 2017;5(4):956-64.e3.
6. Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, Humbert M, Jones P, Gibson PG, Vestbo J, Beasley R, Pavord ID. Treatable traits: toward precision medicine of chronic airway diseases. Eur Respir J. 2016;47(2):410-9.
7. Gibson PG, McDonald VM, Marks GB. Asthma in older adults. Lancet. 2010;376(9743):803-13.
8. Hernán MA, Hernández-Díaz S, Werler MM, Mitchell AA. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. Am J Epidemiol. 2002;155(2):176-84.
9. Robins JM. Data, design, and background knowledge in etiologic inference. Epidemiology. 2001;12(3):313-20.
10. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. BMC Med Res Methodol. 2008;8(1):70.
11. Hoeting JA, Madigan D, Raftery AE, Volinsky CT. Bayesian model averaging: A tutorial. Statistical Science. 1999;14(4):382-401.
12. Raftery A, Hoeting J, Volinsky C, Painter I, Yeung KY. BMA: Bayesian Model Averaging 2017. Available from: https://cran.r-project.org/web/packages/BMA/.

Figure S1 Directed acyclic graph showing relationships between treatable traits in predicting exacerbations

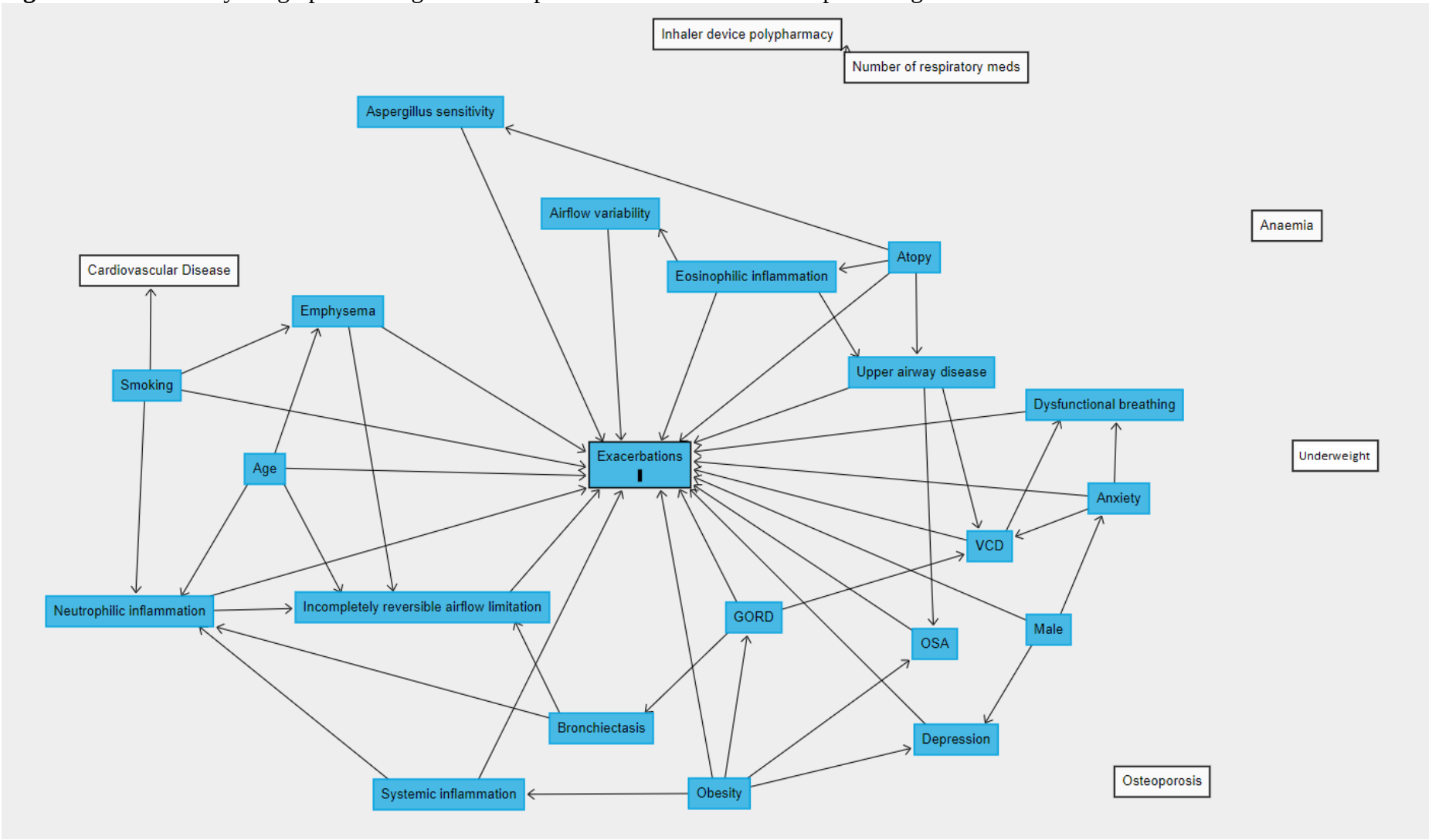


Table S1 Correlation between traits, with positive correlations denoted in blue and negative correlations in orange (darker = stronger correlation).

	AFL	AF var	Eos	Neu	BE	Emp	Exac	UA	GORD	VCD	Dys Br	OSA	CVD	Ost	Dep	Anx	Ob	Uw	SI	An	IDP	Smo	AS
AFL	-																						
AF var	0.03	-																					
Eos	-0.02	0.02	-																				
Neu	0.28	0.01	-0.16	-																			
BE	0.06	-0.13	0.08	0.09	-																		
Emp	0.10	-0.02	0.05	0.06	0.03	-																	
Exac	-0.02	0.03	0.07	0.13	0.03	-0.01	-																
UA	-0.09	0.03	0.07	0.00	0.00	-0.10	0.09	-															
GORD	0.07	-0.08	0.03	0.07	0.03	0.07	0.05	0.09	-														
VCD	-0.08	-0.06	0.00	-0.13	0.04	-0.03	0.09	0.06	0.11	-													
Dys br	-0.01	0.02	0.02	.	0.05	-0.02	0.12	0.11	0.08	0.20	-												
OSA	0.01	0.06	-0.04	0.17	0.00	-0.01	0.09	-0.05	0.06	0.03	0.08	-											
CVD	0.08	-0.19	-0.01	0.13	-0.05	0.01	-0.06	-0.11	0.19	0.07	-0.05	0.03	-										
Ost	0.13	-0.05	0.05	0.00	0.02	0.00	0.14	-0.01	0.08	0.15	0.13	0.02	0.04	-									
Dep	-0.06	0.09	0.06	-0.04	0.00	0.06	0.20	0.04	0.05	0.09	0.10	0.08	-0.08	0.03	-								
Anx	-0.15	-0.04	0.05	-0.15	0.05	0.01	0.15	0.06	-0.01	0.06	0.09	0.10	-0.09	-0.04	0.51	-							
Ob	-0.08	0.04	-0.05	0.20	-0.01	-0.03	0.11	-0.02	0.12	0.04	0.02	0.26	0.10	0.02	0.11	0.05	-						
Uw	-0.07	-0.02	0.05	-0.04	-0.02	-0.01	0.09	0.06	-0.02	-0.02	-0.01	-0.03	0.00	0.05	-0.04	0.02	-0.08	-					
SI	0.08	0.02	0.07	0.06	0.05	0.09	0.25	0.12	0.10	0.01	0.00	0.03	-0.06	0.09	0.09	0.04	0.12	0.01	-				
An	-0.07	0.02	-0.11	0.07	-0.04	0.00	-0.01	-0.08	-0.06	0.05	-0.02	0.07	0.13	0.14	0.11	0.00	0.09	-0.01	0.02	-			
IDP	0.07	-0.03	-0.02	0.00	-0.02	0.03	0.11	0.03	0.12	0.03	0.02	-0.03	0.01	0.08	0.03	-0.02	0.06	0.01	0.07	0.00	-		
Smo	0.02	0.01	-0.08	-0.01	-0.01	-0.03	0.10	0.05	0.02	-0.05	0.02	-0.03	0.00	0.01	0.09	0.02	-0.03	-0.02	0.13	0.01	0.06	-	
AS	0.13	0.10	0.06	-0.01	-0.04	-0.06	-0.04	0.07	-0.09	0.08	-0.02	-0.09	0.04	0.10	-0.01	-0.01	-0.02	-0.11	-0.01	0.08	-0.01	0.04	-
Asp	0.15	-0.06	0.02	0.08	0.14	-0.02	0.00	-0.05	0.04	0.04	-0.03	-0.03	0.05	0.16	-0.05	-0.04	-0.07	0.07	0.11	0.09	0.08	-0.03	0.29

Key:

AFL: Incompletely reversible airflow limitation
AF var: airflow variability
Eos: Eosinophilic inflammation
Neu: Neutrophilic inflammation
BE: Bronchiectasis
Emp: Emphysema
Exac: Exacerbation prone
UA: Upper airway disease
Dys br: Dysfunctional breathing
OSA: Obstructive sleep apnoea
CVD: Cardiovascular disease
Ost; Osteoporosis
Dep: depression
Anx: Anxiety
Ob: obesity
Uw: Underweight
SI: systemic inflammation
An: Anaemia
IDP: Inhaler-device polypharmacy
Smo: Smoking
AS: Allergic sensitisation
Asp: Aspergillus sensitisation

Table S2 Proportion agreement and kappa interrater reliability of two independent coders (KG, SAH) of each treatable trait within a subset of SAWD participants (N = 343).

Treatable trait	Agreement	Kappa	SE
Pulmonary traits			
Incompletely reversible airflow limitation	97.74%	0.95	0.06
Airflow variability	97.38%	0.92	0.07
Eosinophilic inflammation	97.56%	0.95	0.06
Neutrophilic inflammation	96.81%	0.88	0.10
Bronchiectasis	98.83%	0.88	0.05
Emphysema	99.42%	0.80	0.05
Frequent exacerbations	96.50%	0.93	0.05
Extrapulmonary traits			
Upper airway disease	85.13%	0.71	0.05
GORD	90.38%	0.81	0.05
VCD	99.13%	0.93	0.05
Dysfunctional breathing	99.71%	0.91	0.05
OSA	96.21%	0.85	0.05
Cardiovascular disease	88.34%	0.74	0.05
Osteoporosis	97.96%	0.90	0.05
Depression	99.70%	0.99	0.06
Anxiety	99.70%	0.99	0.06
Obesity	99.12%	0.98	0.05
Underweight	100.00%	1.00	0.05
Systemic inflammation	99.69%	0.99	0.06
Anaemia	99.34%	0.98	0.06
Behavioural traits and risk factors			
Inhaler-device polypharmacy*	83.38%	0.51	0.05
Smoking	100.00%	1.00	0.05
Allergic sensitisation	96.31%	0.88	0.06
Aspergillus sensitisation	91.51%	0.80	0.06

Footnotes:

*One coder excluded and other coder included nasal-steroid inhalers, which partly explains the low kappa value.

GORD: gastro-oesophageal reflux disease; OSA: obstructive sleep apnoea; SE: standard error; VCD: vocal cord dysfunction.

Table S3 Exacerbations at baseline and across follow-up by severity status.

	Severe asthma		Non-severe asthma		*p*
EXACERBATIONS BEFORE BASELINE (*N* = 536)					
Exacerbation type in the 12 months before baseline					
Oral corticosteroid use, N (%)	306	(70.5)	30	(29.4)	<0.001
Unscheduled visits to the doctor, N (%)	199	(45.9)	27	(26.5)	<0.001
Emergency room visits, N (%)	104	(24.0)	4	(3.9)	<0.001
Hospitalisations, N (%)	96	(22.1)	2	(2.0)	<0.001
Intravenous corticosteroid, N (%)	42	(9.7)	2	(2.0)	0.008
Intensive care admissions, N (%)	19	(4.4)	0	(0.0)	0.032
Number of oral corticosteroid courses in past year, median (IQR)	2	(0, 4)	0	(0, 1)	<0.001
EXACERBATIONS DURING FOLLOW-UP (6-24 months post-baseline; *N* = 354)					
Any exacerbation during follow-up, N (%)	209	(70.6)	25	(43.1)	<0.001
Frequent exacerbations (2 or more per year), N (%)	197	(68.6)	24	(42.1)	<0.001
Number of exacerbations per year, median annualised rate (IQR)	2	(0, 4)	0	(0, 2)	<0.001
Exacerbation type during follow-up period					
Oral corticosteroid use, N (%)	159	(53.0)	13	(22.4)	<0.001
Unscheduled visits to the doctor, N (%)	115	(38.3)	12	(20.7)	0.011
Emergency room visits, N (%)	42	(14.0)	1	(1.7)	0.007
Hospitalisations, N (%)	41	(13.7)	0	(0.0)	0.001
Intravenous corticosteroid, N (%)	28	(9.3)	2	(3.4)	0.195
Intensive care admissions, N (%)	3	(1.0)	0	(0.0)	.

p from Fisher's exact test

Table S4 Association between continuous traits at baseline and exacerbations over follow-up (6-24 months).

Variable	**IRR**	**95% CI**	***p***
Post BD FEV1/FVC	3.96	(0.65, 24.16)	0.136
Post BD FEV1 (L)	0.91	(0.76, 1.08)	0.277
Log blood eosinophil count (10^9/L)	1.02	(0.94, 1.11)	0.614
Log sputum eosinophils (%)	1.03	(0.95, 1.12)	0.519
FENO (parts per billion)	1.00	(1.00, 1.01)	0.502
Sputum neutrophils (%)	1.00	(1.00, 1.01)	<0.001
Number of exacerbations before baseline	1.21	(1.10, 1.33)	<0.001
HADS depression score	1.07	(1.05, 1.08)	<0.001
HADS anxiety score	1.04	(1.02, 1.06)	<0.001
BMI (continuous; kg/m^2)	1.00	(0.99, 1.02)	0.670
BMI (categories)			
Healthy BMI	reference		
Underweight	1.25	(0.83, 1.88)	0.284
Overweight	0.87	(0.66, 1.15)	0.315
Obese	1.02	(0.72, 1.45)	0.916
Log while blood cell count (10^9/L)	1.51	(1.00, 2.28)	0.053
Haemoglobin (g/L)	1.00	(0.99, 1.00)	0.615
Number of inhaler devices	1.31	(1.16, 1.47)	<0.001
Exhaled carbon monoxide (parts per million)	1.03	(0.99, 1.07)	0.098

BD: bronchodilator; BMI: Body mass index; CI: confidence interval; FENO: Fractional Exhaled Nitric Oxide; FEV1: Forced expiratory volume in 1 second; FVC: forced vital capacity; HADS: Hospital Anxiety and Depression Scale; IRR: incident rate ratio.

Table S5 Pooled incident rate ratios (IRR) and 95% confidence intervals (95% CI) and posterior inclusion probability (PIP) in models (Bayesian Model Averaging).

Predictors	**IRR**	**(95% CI)**	**PIP (%)**
Exacerbation prone	1.96	(1.93, 1.99)	100.0
Log(Assessments completed)	5.36	(5.25, 5.48)	100.0
Inhaler device polypharmacy	1.28	(1.25, 1.31)	69.1
OSA	1.22	(1.19, 1.25)	50.3
Age	1.00	(1.00, 1.00)	34.5
Depression	1.10	(1.08, 1.12)	27.9
VCD	1.06	(1.04, 1.08)	14.2
Allergic sensitisation	0.98	(0.97, 0.98)	11.1
Male	0.99	(0.98, 0.99)	6.6
Dysfunctional breathing	1.03	(1.01, 1.05)	6.1
Incompletely reversible AFL	0.99	(0.99, 1.00)	4.0
Smoking	1.01	(1.00, 1.02)	3.5
Anxiety	1.01	(1.00, 1.01)	3.3
Anaemia	0.99	(0.99, 1.00)	2.5
Airflow variability	1.00	(1.00, 1.01)	2.4
Upper airway disease	1.00	(1.00, 1.01)	2.4
GORD	1.00	(1.00, 1.00)	1.8
Bronchiectasis	1.00	(1.00, 1.01)	1.7
Number of respiratory medications	1.00	(1.00, 1.00)	1.7
Aspergillus sensitivity	1.00	(1.00, 1.00)	1.0
Systemic inflammation	1.00	(1.00, 1.00)	0.9
Obesity	1.00	(1.00, 1.00)	0.7
Eosinophilic inflammation	1.00	(1.00, 1.00)	0.6
Neutrophilic inflammation	1.00	(1.00, 1.00)	0.6
Cardiovascular disease	1.00	(1.00, 1.00)	0.6
Osteoporosis	1.00	(1.00, 1.00)	0.6
Underweight	1.00	(0.99, 1.01)	0.5
Emphysema	1.00	(1.00, 1.00)	0.3

AFL: airflow limitation; CI: confidence interval; GORD: gastro-oesophageal reflux disease; IRR: incident rate ratio; OSA: obstructive sleep apnoea; VCD: vocal cord dysfunction.

eatable Traits predict future attacks in severe asthm

eatable Traits'
been proposed
new paradigm
airway disease
anagement.

T few available
a characterize
eatable traits'
vere asthma, or
eir impact on
future risk.

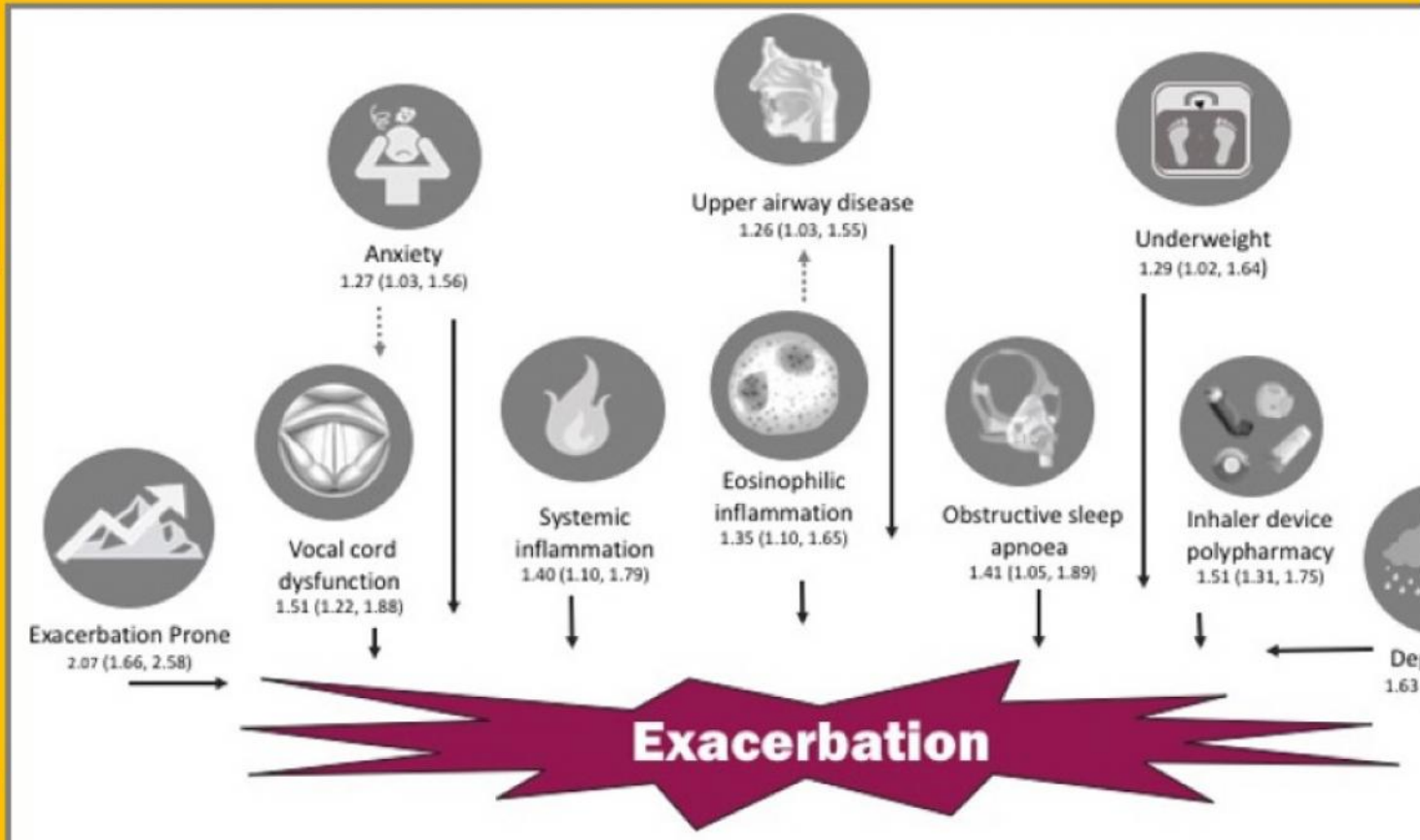
We identified that 24 traits were assessed in a registry (*N* = 536)

People with severe asthma expressed 29% of traits

People with non-severe asthma expressed 19% of traits

Each additional trait present:
13% ↑ risk of attacks

Greater disease burden in severe asthma



Incident rate ratios (95% confidence interval) showing degree that each trait is associated with future exa

espirology

Treatable traits can be identified in a severe asthma registry and predict future exacerbations

McDonald et al. Respirology 2018; DOI: 10.1111/r