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

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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.

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.

Methods

The Australasian Severe Asthma Web-based Database (SAWD) enrolled 434 participants with severe asthma and a comparison group of 102 with non-severe asthma. Published treatable traits were mapped to registry data fields and their prevalence described. Participants were characterised at baseline and each 6 months for 24 months.

Results

In SAWD, 24 treatable traits were identified in three domains: pulmonary, extrapulmonary and behavioural/risk-factors. People with severe asthma expressed more pulmonary and extrapulmonary treatable traits than non-severe asthma. Allergic sensitisation, 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

Severe asthma; comorbidity; registry; treatable traits; exacerbation

Short title

Treatable traits in severe asthma

INTRODUCTION

Severe asthma is a heterogeneous disease of the airways that is complicated by frequent attacks and comorbidities. A 2017 Lancet commission proposed that the current concept of airway diseases fails to recognize the complexity of disease and does little to promote individualised management.[1] To address this issue, a new approach has been proposed that characterises 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. Secondly, to assess the prevalence of treatable traits in severe asthma compared with non-severe asthma, and finally to assess the relationship between treatable traits and future exacerbation risk. We hypothesised that treatable traits could be recognised 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 (Supplementary Appendix S1). Inhalation technique, education, adherence and written action plan (WAP) had to be optimised 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.

Registry assessments

Demographic characteristics, medication use, asthma and comorbidity history, asthma control (ACQ6[8]), asthma quality of life (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 (FeNO) and induced sputum were optional. Past-year exacerbations were identified using a standardised assessment as defined previously.[11] Additional clinical investigations performed within the last five years were logged in the database, including polysomnography, 24h 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 correlation were performed to examine the intercorrelation between multiple traits (Supplementary Table S1).

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]; Supplementary Appendix S1 and Figure S1). 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). 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 (PIP).

BMA was conducted in the R programming environment (R Foundation, 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, USA). The significance level for frequentist analyses was set at 0.05.

RESULTS

Baseline characteristics

There were 434 individuals with severe and 102 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] Since asthma-management skills were optimised in the severe asthma group prior to registry entry, these traits were excluded from analysis. Bacterial colonisation 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 (KG, SH). Inter-rater reliability was very high for most traits (agreement 92-100%; kappa 0.78-1.00), 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) (Supplementry Table S2).

Treatable traits prevalence

The median (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) (Figure 1A). Individuals with severe asthma had more pulmonary (33%, IQR 17-50%) and extrapulmonary traits (25%, IQR 15-38%) compared with non-severe (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 disorder (GORD), inhaler-device polypharmacy and Aspergillus sensitisation (Table 2).

Treatable traits and exacerbation risk

The severe asthma group reported more baseline past-year exacerbations (p<0.001), irrespective of exacerbation type (Supplementary Table S3). 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 (Supplementary Figure S1). 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 summarised as the incidence rate ratio (IRR). For each additional trait present, there was a 14% 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 (Supplementary Table S4)

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 and number of follow-up visits completed, inhaler-device polypharmacy, OSA, age and depression emerged as the best predictors of exacerbation risk in people with severe asthma (Figure 3, Supplementary Table S5).

DISCUSSION

Using a severe asthma registry database, we identified the prevalence of 24 treatable traits. Many pulmonary 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 individualised management. This definition is consistent with the concepts described by Agusti *et al*.[3] and in our prior work.[6] Of the 24 traits we identified in the registry, five were not included in the Agusti proposal: prone to exacerbation, neutrophilic inflammation, Aspergillus sensitisation, 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 characterisation studies of other severe asthma cohorts have been previously published,[16-21] but reporting of comorbidities 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 sensitisation, 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. These data should be interpreted with caution however, 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 optimised 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 2.33 times that of non-severe. 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 (Supplementary Figure S1). This novel analysis identified traits associated with increased exacerbation risk including VCD, raising 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 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 assessment 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 RCTs 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 recognise that severe asthma is a heterogeneous disease associated with multiple comorbidities and behavioral 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 comorbidities may have under- 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 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 isn't a treatable trait,

for example is airflow limitation in severe asthma treatable? We propose that further international consensus is required to determine accepted treatable traits and their biomarkers.

In conclusion, we have demonstrated that data collected after systematic characterisation 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'.

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Author contribution statement

VMMcD, KG and PGG concieved the research question. SAH performed the analysis. VMMcD and PGG 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

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Figure captions

Figure 1. Treatable traits in severe and non-severe asthma. (A) Median proportion of treatable traits present (± interquartile range) in the severe and non-severe asthma groups. Prevalence of treatable traits, separated as (B) pulmonary traits, (C) extrapulmonary traits, and (D) behavioural traits and risk-factors. * $p<0.05$; ** $p<0.01$; *** $p<0.001$. GORD: gastro-oesophageal reflux disease; 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 confidence intervals for the total effect of each trait on exacerbations over time.

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 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.

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)	
Ex-smoker	149	(34.7)	34	(34.0)	0.223
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 FEV1, % predicted, mean (SD)	66.9	(21.2)	79.7	(19.4)	<0.001
Pre-bronchodilator FEV1/FVC, mean (SD)	0.8	(0.2)	0.9	(0.1)	<0.001
Post-bronchodilator FEV1, %	73.1	(21.9)	83.5	(19.3)	<0.001

predicted, mean (SD)					
Post-bronchodilator FEV1/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 hospitalised, 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; BD: bronchodilator; BDP: beclomethasone dipropionate; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroids.

Table 2. Treatable traits assessment and prevalence.

Treatable traits	Assessment tool	Guide for identification	Severe asthma		Non-severe asthma		*p*
			N expressed / N assessed	%	N expressed/ N assessed	%	
Pulmonary traits							
Incompletely reversible AFL	Spirometry	Post-bronchodilator FEV1/FVC < 0.7	183/314	(58.3)	34/87	(39.1)	0.002
Airflow variability[#]	Spirometry	FEV1 ≥200mL and ≥12% post-bronchodilator	63/255	(24.7)	15/83	(18.1)	0.233
Eosinophilic inflammation	Induced sputum FeNO	Sputum eosinophils ≥ 3% and/or FeNO ≥ 30ppb and/or blood eosinophils ≥ 0.3 x 10^9/L	210/397	(52.9)	54/90	(60.0)	0.242

	FBC						
***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 x 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	Medication	Prescription of 3 or more different	126/431	(29.2)	18/102	(17.6)	0.018

polypharmacy[¥]	review	inhalers					
Smoking	Self-report Exhaled CO	Report current smoking and/or exhaled CO ≥ 10ppm	20/429	(4.7)	1/100	(1.0)	0.149
Allergic sensitisation	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 sensitisation**	Specific IgE SPT	Immunocap or SPT positive to aspergillus extract	117/302	(38.7)	16/83	(19.3)	0.001

Percentages calculated on nonmissing data. *: Identified in Gibson *et al*.[2] only, with remainder identified in Agusti *et al*.[3] or both; [#]: Demonstrable within 7 days of first assessment; [§]: Allergic rhinitis, nasal polyps and sinusitis; [¶]: Includes hypertension; [¥]: Based on use of the following inhaler types: pressurised metered device inhaler, Turbuhaler, Accuhaler, Autohaler, Aeroliser, Handihaler, Breezhaler, Respimat, Ellipta, Genuair and nasal steroid inhaler.

AFL: airflow limitation; BMI: body mass index; CO: carbon monoxide; CT: computed tomography; FBC: full blood count; FeNO: exhaled nitric oxide fraction; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; GORD: gastro-oesophageal reflux disease; HADS: Hospital Anxiety and Depression Scale; Hb: haemoglobin; IgE: Immunoglobulin E; OSA: obstructive sleep apnoea; PSG: polysomnography; SPT: skin prick test; VCD: vocal cord dysfunction.

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

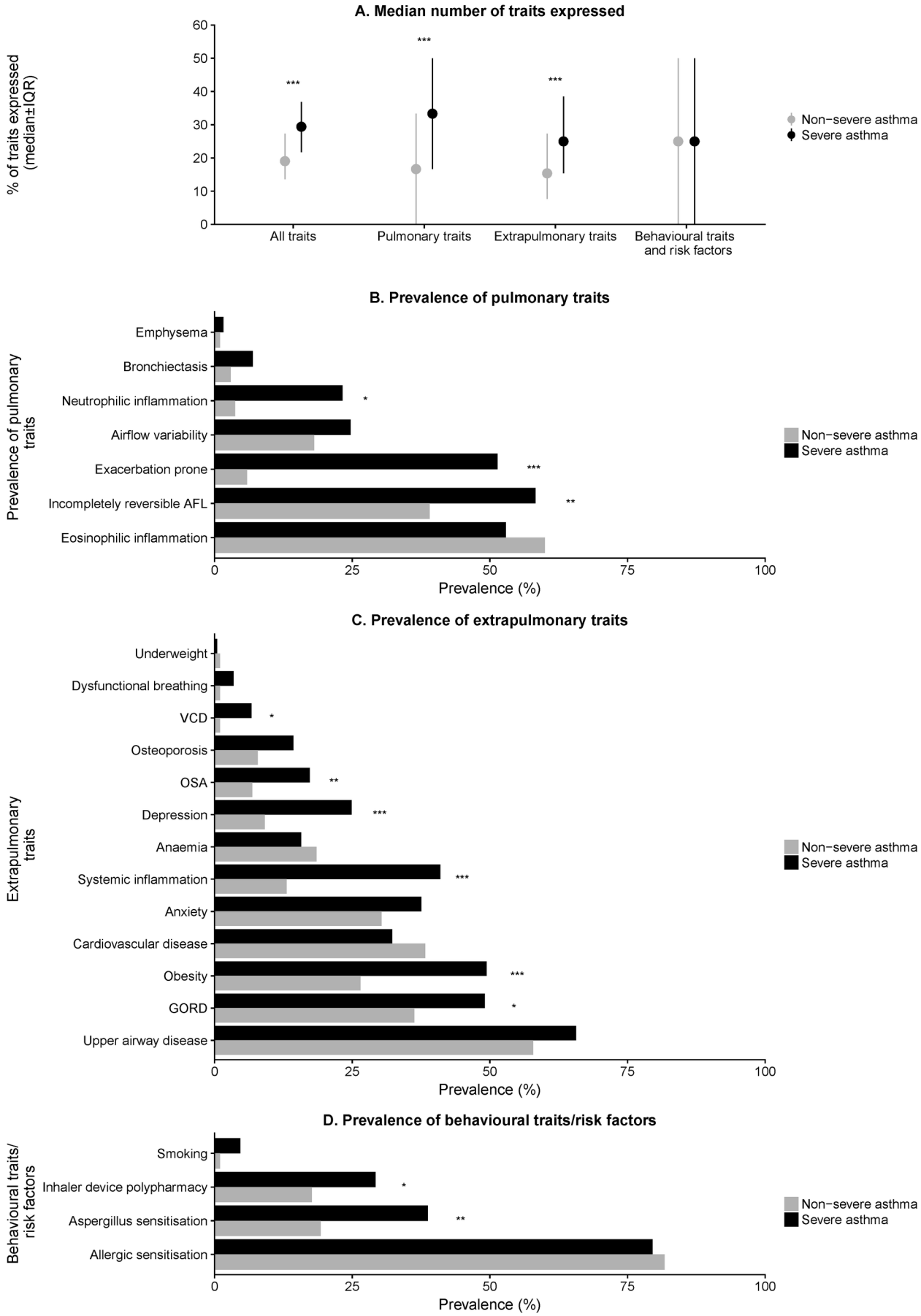
Asthma characteristics and treatable traits	Unadjusted IRR	95% CI	*p*	Adjusted IRR	95% CI	*p*	Covariates in adjusted analyses*
Asthma characteristics							
Severe asthma (reference: non-severe asthma)	2.36	(1.93, 2.90)	<0.001				
ACQ6	1.46	(1.34, 1.59)	<0.001				
All treatable traits							
Total number 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 sensitisation.
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 sensitisation, 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 sensitisation	1.03	(0.77, 1.38)	0.828	1.03	(0.77, 1.38)	0.828	None.
Aspergillus sensitisation	1.17	(0.92, 1.48)	0.206	1.18	(0.81, 1.71)	0.393	Allergic sensitisation.
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 (Supplementary Figure S1), 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; OSA: obstructive sleep apnoea; VCD: vocal cord dysfunction.



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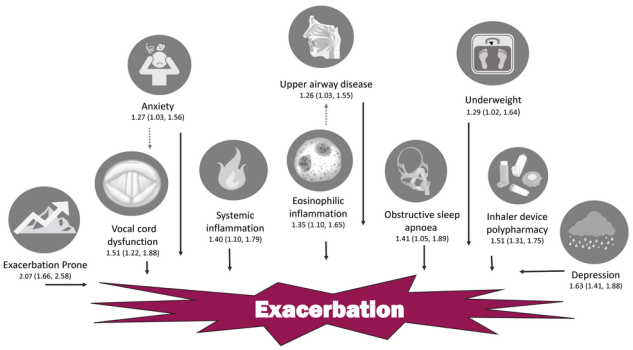

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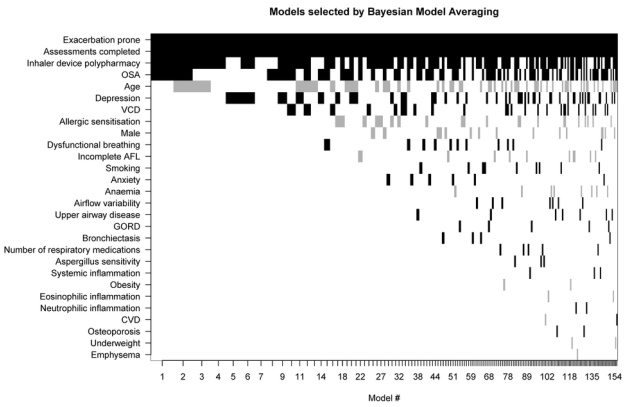

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