

Treatable Traits in the European U-BIOPRED Adult Asthma Cohorts

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1 1 Treatable Traits in the European U-BIOPRED Adult Asthma Cohorts
2 2
3 3 To the Editor
4 4
5 5 Improvements in asthma outcomes have stalled over the past decade (1), which may be attributed to
6 6 treating patients on the basis of a generic diagnostic label. The taxonomy 'Treatable Traits' was proposed
7 7 by Agusti and colleagues (2016) as a precision medicine approach for the diagnosis and management of
8 8 chronic airway diseases that is based on the identification of genetic, phenotypic and psychosocial
9 9 characteristics for which therapeutic interventions are known to improve respiratory health (2). The
10 10 Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) project was set up
11 11 to identify multi-dimensional phenotypes and endotypes in severe asthma (3). Here, we aim to identify and
12 12 quantify treatable traits within the severe and mild/moderate U-BIOPRED adult asthma cohorts (3) and
13 13 across previously identified phenotypes (4). We hypothesise that treatable traits will be more common in
14 14 severe asthma and vary significantly across asthma phenotypes.

15 15 Data from the severe asthma and mild–moderate asthma cohorts of the U-BIOPRED project were included
16 16 in this study. Full details of the study population and methodology have been presented elsewhere (3).

17 17 Criteria for treatable traits were based on Agusti *et al.*, (2) and presented in table 1. Chi Square tests were
18 18 used to examine differences in the prevalence of each treatable trait between groups and independent
19 19 sample t-tests used to determine differences in the total number of traits between cohorts. No adjustment
20 20 for multiple testing was applied as the analyses were considered exploratory; as this may inflate the type-1
21 21 error rate individual p values are presented for each comparison. A post-hoc power calculation shows our
22 22 sample of 421 (severe smoking/ex-smoking vs. severe non-smoking) and 399 (severe non-smoking vs.
23 23 mild/moderate) is sufficient to identify a difference in treatable trait prevalence between cohorts with a
24 24 medium effect size (0.3) and a power close to 1.00. Data analysis was supported by SPSS (Version 24), with
25 25 significance set at $p < 0.05$, unless otherwise stated.

26

1 1 **Prevalence of treatable traits**

2 2 Twenty-three treatable traits were identified, including seven pulmonary, 11 extra-pulmonary and five
3 3 behavioural / psychosocial treatable traits (table 2). Seven out of the ten most prevalent traits in severe
4 4 asthma were classed as pulmonary treatable traits. The most prevalent extra-pulmonary traits were: atopy,
5 5 rhinosinusitis, obesity, reflux and obstructive sleep apnoea. Poor adherence to medication, anxiety and
6 6 depression were the most common behavioural / psychosocial treatable traits in severe asthma.

7

8 8 **Differences in treatable traits across asthma cohorts**

9 9 The severe smoking/ex-smoking asthma cohort displayed on average one more treatable trait than the
10 10 severe non-smoking asthma cohort (8 ± 3 vs. 7 ± 2 , $p=0.007$). Differences in the prevalence of individual
11 11 traits, all higher in the smoking/ex-smoking cohort, were seen in bronchodilator reversibility, fixed airflow
12 12 limitation ($p=0.050$), reflux, cardiovascular disease and psychiatric disease. Only atopy was higher in
13 13 prevalence in the non-smoking cohort.

14

15 15 Non-smoking individuals with severe asthma have more treatable traits than non-smoking individuals with
16 16 mild/moderate asthma (7 ± 2 vs. 5 ± 2 , $p<0.001$). Likewise, individual treatable traits were generally more
17 17 common in non-smoking severe asthma compared to the mild/moderate asthma cohort. Only in atopy and
18 18 poor medication adherence was the prevalence of the treatable trait significantly higher in mild/moderate
19 19 asthma. The prevalence of treatable traits across previously identified clusters (4) are presented and
20 20 discussed on the online supplementary material.

21

22 22 **Discussion**

23 23 The identification of treatable traits facilitates a precision medicine strategy for the management of airways
24 24 disease, that is free from the traditional diagnostic labels and based on the identification of pulmonary,
25 25 extra-pulmonary and psychosocial characteristics, for which there are evidence based therapeutic choices.
26 26 This proposal was recently supported by the *Lancet* commission 'After asthma: redefining airways disease'
27 27 (5) and was a favoured strategy to move the field towards precision medicine at a research seminar, held at

1 the European Respiratory Society's annual meeting (6). Ours is the first study to apply the concept to a
2 large asthma cohort and we have identified a plethora of pulmonary, extra-pulmonary and behavioural /
3 psychosocial treatable traits. The prevalence of treatable traits, both pulmonary and non-pulmonary, was
4 generally higher in individuals with severe asthma compared to mild/moderate asthma. We also identified
5 a difference in the prevalence of pulmonary treatable traits across clinical clusters of patients.
6 Approximately 5-10% of asthmatics remain poorly controlled, despite being prescribed the maximum dose
7 of therapy (7). Our data suggest individuals with severe asthma, who remain symptomatic despite receiving
8 a high dose ICS, display on average seven treatable traits, and therefore present multiple treatment
9 opportunities beyond the traditional stepwise approach.

10 Perhaps unsurprisingly, pulmonary traits accounted for seven of the ten most prevalent treatable traits in
11 our asthma cohorts and were generally more common in severe asthma. Interestingly however, we also
12 observed an increased prevalence of extra-pulmonary and behavioural/psychosocial traits in severe asthma
13 suggesting an association with asthma severity, which may reflect the impact of living with severe chronic
14 respiratory conditions. Our data highlight that multiple treatment opportunities exist beyond the
15 pulmonary system, and a holistic management strategy, such as the treatable trait approach, may be
16 beneficial to both physical and mental well-being.

17 This is the first study to apply the concept of treatable traits to a large asthma cohort. Several limitations
18 are worthy of discussion; firstly we utilised the original paper on treatable traits (2), treatment guidelines
19 and clinical experience to determine the classification criteria for our treatable traits. We acknowledge that
20 our list of traits is not exhaustive and that the selected criteria for some traits could be contentious.
21 Prospective studies would benefit from additional paraclinical investigations to determine the prevalence
22 of additional treatable traits, for example; ventilation heterogeneity and small airway disease. Finally, we
23 acknowledge that some traits may not be mutually exclusive and some maybe modified by asthma
24 treatment. Associations between traits were not explored here, but have been discussed elsewhere (8).

25 In conclusion, the label-free, precision medicine approach provided by the treatable traits construct
26 allowed for the identification of multiple treatment opportunities for patients with asthma, beyond the

1 1 traditional step-wise approach. We eagerly await the results of prospective, longitudinal, clinical trials to
2 2 determine whether this translates to improved clinical outcomes for individuals with respiratory disease.

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33 AJS and SJF had full access to all of the data in the study and take responsibility for the integrity of the data
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52 **Conflicts of interests:**
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1 1 Dr Simpson has nothing to disclose; Dr. Hekking has nothing to disclose; Dr Shaw reports advisory board
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1 4 **Table 1.** Treatable traits and defining criteria
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Treatable trait category	Treatable trait	Defining criteria
Pulmonary	Fixed airflow limitation	Post-bronchodilator $FEV_1/FVC < 0.7$
	Bronchodilator reversibility	Post-bronchodilator increase in FEV_1 <u>AND/OR</u> $FVC \geq 12\%$ <u>AND</u> ≥ 200 ml
	Type 2 inflammation	Sputum eosinophil count $\geq 2\%$ <u>AND/OR</u> blood eosinophils ≥ 450 cells per μl <u>AND/OR</u> $FeNO > 50$ ppb
	Neutrophilic inflammation	Sputum neutrophil count $> 60\%$
	Cough	Asthma Quality of Life Questionnaire (AQLQ) Question 12 score ≤ 4 <u>AND/OR</u> Sino-Nasal Outcomes Test (SNOT-20) Question score 4 ≥ 3
	Exercise-induced respiratory symptoms	Medical history finding of "routine physical activity and/or physical exercise as asthma trigger"
	Bronchitis	Medical history finding of "Current <u>AND/OR</u> chronic bronchitis"
Extra-pulmonary	Rhinosinusitis	Medical history finding of "Allergic/Non-allergic rhinitis active <u>AND/OR</u> sinusitis active"
	Nasal polyps	Medical history finding of "Nasal polyps active"
	Obese	$BMI > 30$
	Underweight	$BMI < 18.5$
	Obstructive sleep apnoea	Epworth sleepiness scale score ≥ 11
	Reflux	Medical history finding of "Reflux active"
	Vocal cord dysfunction	Medical history finding of "Vocal Cord Dysfunction active"
	Osteoporosis	Medical history finding of "Osteoporosis active"
	Cardiovascular disease	Medical history finding of "Coronary disease active"
	Eczema	Medical history finding of "Eczema active"
Behavioural / Psychosocial	Atopic	Positive skin prick test <u>AND/OR</u> blood IgE result
	Smoking	Medical history finding of "Current smoker"
	Poor medication adherence	Medication Adherence Rating Scale (MARS) mean score < 4.5
	Psychiatric disease	Medical history finding of "Psychiatric disease active"
	Depression	Hospital Anxiety and Depression (HADS) depression domain score ≥ 11
	Anxiety	Hospital Anxiety and Depression (HADS) anxiety domain score ≥ 11

2 3 Treatable traits presented here are based on that of Agusti et al.,(2). FEV_1 , Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; $FeNO$, Fraction of Exhaled Nitric Oxide; BMI, Body Mass Index.

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4 **Table 2.** Frequency of treatable traits in severe and mild/moderate asthma, ordered by trait category and then trait frequency in severe asthma cohort.

Trait category	Treatable Trait	Severe asthma (combined)	Severe smoking/ex-smoking asthma	Severe non-smoking asthma	Mild/Moderate non-smoking asthma	Severe smoking/ex-smoking vs. severe non-smoking asthma	Mild/moderate vs. severe non-smoking
	Subjects, n	421	110	311	88		
Pulmonary	Exercise-Induced Respiratory symptoms, n (%)	352/421 (84)	91/110 (83)	261/311 (84)	56/88 (64)	P=0.085	P<0.001
	Cough, n (%)	246/387 (64)	65/98 (66)	181/289 (63)	19/87 (22)	P=0.511	P<0.001
	Fixed airflow limitation, n (%)	245/415 (59)	73/109 (67)	172/306 (56)	17/85 (20)	P=0.050	P<0.001
	Bronchodilator reversibility, n (%)	244/415 (59)	74/109 (68)	170/306 (56)	33/85 (39)	P=0.025	P=0.006
	Bronchitis, n (%)	214/421 (51)	57/110 (52)	157/311 (51)	16/88 (18)	P=0.810	P<0.001
	Type 2 inflammation, n (%)	184/421 (44)	50/110 (45)	134/311 (43)	30/88 (34)	P=0.667	P=0.130
	Neutrophilic inflammation, n (%)	73/181 (40)	20/53 (38)	53/128 (41)	13/43 (30)	P=0.647	P=0.193
Extra-pulmonary	Atopic, n (%)	298/421 (71)	68/110 (62)	230/311 (74)	79/88 (90)	P=0.016	P=0.002
	Rhinosinusitis, n (%)	204/421 (48)	48/110 (44)	156/311 (50)	35/88 (40)	P=0.239	P=0.085
	Obese, n (%)	164/421 (39)	44/110 (40)	120/311 (39)	16/88 (18)	P=0.794	P<0.001
	Reflux, n (%)	152/421 (36)	50/110 (46)	102/311 (33)	10/88 (11)	P=0.018	P<0.001
	Obstructive sleep apnoea, n (%)	95/372 (26)	26/95 (27)	69/277 (25)	9/85 (11)	P=0.635	P=0.005
	Osteoporosis, n (%)	94/421 (22)	24/110 (22)	70/311 (23)	3/88 (3)	P=0.881	P<0.001
	Eczema, n (%)	76/421 (18)	19/110 (17)	57/311 (18)	10/88 (11)	P=0.805	P=0.123
	Nasal polyps, n (%)	58/421 (14)	14/110 (13)	44/311 (14)	1/88 (1)	P=0.710	P=0.001
	Vocal cord dysfunction, n (%)	17/421 (4)	5/110 (5)	12/311 (4)	1/88 (1)	P=0.753	P=0.204
	Cardiovascular disease, n (%)	9/421 (2)	5/110 (5)	4/311 (1)	0/88 (0)	P=0.042	P=0.285
	Underweight, n (%)	2/421 (1)	0/110 (0)	2/311 (1)	2/88(2)	P=0.399	P=0.175
Behavioural / Psychosocial	Poor medication adherence, n (%)	147/372 (40)	38/94 (40)	109/278 (39)	44/84 (52)	P=0.835	P=0.032
	Anxiety, n (%)	65/295 (22)	16/72 (22)	49/223 (22)	4/70 (6)	P=0.965	P=0.002
	Depression, n (%)	39/295 (13)	13/72 (18)	26/223 (12)	2/70 (3)	P=0.164	P=0.029
	Smoking, n (%)	42/421 (10)	42/110 (38)	-	-	-	-
	Psychiatric disease, n (%)	32/421 (8)	14/110 (13)	18/311 (6)	0/88 (0)	P=0.018	P=0.021

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33 Data are expressed as n/N (%). Differences between cohorts determined using Chi-Square test

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For Peer Review

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3 Prevalence of treatable traits across phenotypes
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5 Lefaudeux et al., [7] previously identified four clinical clusters in the U-BIOPRED participants. Cluster
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7 One, described by Lefaudeux et al. [7] as well-controlled, moderate-severe asthma, generally had a
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9 lower prevalence of pulmonary and non-pulmonary treatable traits compared with the other
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11 clusters, with the exception of atopy and rhinosinusitis (table 3). Cluster Two, characterised by
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13 severe, late onset asthma [7], had a high prevalence of pulmonary treatable traits such as
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15 bronchodilator reversibility, fixed airflow limitation and type 2 inflammation, and higher levels of
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17 non-pulmonary traits including diabetes, depression and smoking than the other clusters (table 3).
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19 Cluster Three, described as severe, moderate-severe airflow limitation and oral steroid dependence
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21 [7], had the highest prevalence of respiratory symptoms on exertion and neutrophilic inflammation.
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23 Cluster Four, was female predominant, mild-none obstruction and experienced frequent
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25 exacerbations [7]. Similar to cluster three, we observed a very high prevalence of respiratory
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27 symptoms on exertion in cluster four, however unlike cluster three, cluster four was associated with
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29 a much higher prevalence of obesity (table 3).
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Table 3. Prevalence of treatable traits in U-BIOPRED clinical clusters

	CLUSTER 1	CLUSTER 2	CLUSTER 3	CLUSTER 4	Sig.
Brief description, from Lefaudeux et al.,[7]	Moderate-severe, well controlled, medium-to-high ICS, mild-none airflow limitation	Severe, late-onset, smokers, severe airflow obstruction, eosinophilic	Severe, moderate-severe obstruction, oral steroid dependent	Severe, female, mild-none obstruction, frequent exacerbations	
Pulmonary Trait					
Exercise-Induced Respiratory symptoms	74/108 (69%)	69/86 (80%)	92/106 (87%)	101/118 (86%)	P=0.002
Cough	35/108 (32%)	55/86 (64%)	72/106 (68%)	75/118 (64%)	P<0.001
Fixed airflow limitation	23/105 (22%)	72/86 (84%)	96/106 (91%)	29/116 (21%)	P<0.001
Bronchodilator reversibility	41/108 (39%)	67/86 (78%)	70/106 (66%)	59/116 (51%)	P<0.001
Bronchitis	30/108 (28%)	36/86 (42%)	59/106 (56%)	62/118 (53%)	P<0.001
Type 2 inflammation	36/108 (33%)	47/86 (55%)	53/106 (50%)	46/118 (39%)	P=0.009
Neutrophilic inflammation	16/52 (31%)	19/50 (38%)	22/46 (48%)	16/46 (35%)	P=0.356
Extra-pulmonary Trait					
Atopic	98/108 (86%)	52/86 (61%)	84/106 (79%)	85/118 (72%)	P<0.001
Rhinosinusitis	52/108 (48%)	32/86 (37%)	49/106 (46%)	63/118 (53%)	P=0.149
Obese	16/108 (15%)	34/86 (40%)	24/106 (23%)	65/118 (55%)	P<0.001
Reflux	14/108 (13%)	30/86 (35%)	32/106 (30%)	52/118 (44%)	P<0.001
Obstructive sleep apnoea	14/103 (14%)	24/85 (28%)	25/101 (25%)	28/114 (25%)	P=0.077
Osteoporosis	4/108 (4%)	22/86 (26%)	28/106 (26%)	23/118 (20%)	P<0.001
Eczema	17/108 (16%)	13/86 (15%)	20/106 (19%)	14/118 (12%)	P=0.545
Nasal polyps	4/108 (4%)	10/86 (12%)	12/106 (11%)	16/118 (14%)	P=0.077
Vocal cord dysfunction	1/108 (1%)	3/86 (4%)	4/106 (4%)	8/118 (7%)	P=0.152
Cardiovascular disease	0/108 (0%)	1/86 (1%)	4/106 (4%)	2/118 (2%)	P=0.186
Underweight	2/108 (2%)	0/86 (0%)	2/106 (2%)	0/118 (0%)	P=0.278
Behavioural / Psychosocial					
Trait					
Poor medication adherence	48/102 (47%)	33/83 (40%)	45/106 (43%)	37/112 (33%)	P=0.204
Anxiety	11/90 (12%)	9/67 (13%)	19/81 (24%)	22/87 (25%)	P=0.061
Depression	4/90 (4%)	14/67 (21%)	12/81 (15%)	9/87 (10%)	P=0.013
Smoking	2/108 (2%)	24/86 (28%)	5/106 (5%)	7/118 (6%)	P<0.001
Psychiatric disease	1/108 (1%)	9/86 (11%)	6/106 (6%)	8/118 (7%)	P=0.038

Data are expressed as n/N (%). Differences across cohorts determined using Chi-Square tests.