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Article type : Letter to the Editor

Treatable Traits in the European U-BIOPRED Adult Asthma Cohorts

To the Editor

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

Data from the severe asthma and mild–moderate asthma cohorts of the U-BIOPRED project were included in this study. Full details of the study population and methodology have been presented elsewhere (3). Criteria for treatable traits were based on Agusti *et al.*, (2) and presented in table 1. Chi Square tests were used to examine differences in the prevalence of each treatable trait between groups and independent sample t-tests used to determine differences in the total number of traits between cohorts. No adjustment for multiple testing was applied as the analyses were considered exploratory; as this may inflate the type-1 error rate individual p values are presented for each comparison. A post-hoc power calculation shows our sample of 421 (severe smoking/ex-smoking vs. severe non-smoking) and 399 (severe non-smoking vs. mild/moderate) is sufficient to identify a difference in treatable trait prevalence between cohorts with a medium effect size (0.3) and a power close to 1.00. Data analysis was supported by SPSS (Version 24), with significance set at $p < 0.05$, unless otherwise stated.

Prevalence of treatable traits

Twenty-three treatable traits were identified, including seven pulmonary, 11 extra-pulmonary and five behavioural / psychosocial treatable traits (table 2). Seven out of the ten most prevalent traits in severe asthma were classed as pulmonary treatable traits. The most prevalent extra-pulmonary traits were: atopy,

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/all.13629

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rhinosinusitis, obesity, reflux and obstructive sleep apnoea. Poor adherence to medication, anxiety and depression were the most common behavioural / psychosocial treatable traits in severe asthma.

Differences in treatable traits across asthma cohorts

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

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

Discussion

The identification of treatable traits facilitates a precision medicine strategy for the management of airways disease, that is free from the traditional diagnostic labels and based on the identification of pulmonary, extra-pulmonary and psychosocial characteristics, for which there are evidence based therapeutic choices. This proposal was recently supported by the *Lancet* commission 'After asthma: redefining airways disease' (5) and was a favoured strategy to move the field towards precision medicine at a research seminar, held at the European Respiratory Society's annual meeting (6). Ours is the first study to apply the concept to a large asthma cohort and we have identified a plethora of pulmonary, extra-pulmonary and behavioural / psychosocial treatable traits. The prevalence of treatable traits, both pulmonary and non-pulmonary, was generally higher in individuals with severe asthma compared to mild/moderate asthma. We also identified a difference in the prevalence of pulmonary treatable traits across clinical clusters of patients.

Approximately 5-10% of asthmatics remain poorly controlled, despite being prescribed the maximum dose of therapy (7). Our data suggest individuals with severe asthma, who remain symptomatic despite receiving a high dose ICS, display on average seven treatable traits, and therefore present multiple treatment opportunities beyond the traditional stepwise approach.

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

This is the first study to apply the concept of treatable traits to a large asthma cohort. Several limitations are worthy of discussion; firstly we utilised the original paper on treatable traits (2), treatment guidelines and clinical experience to determine the classification criteria for our treatable traits. We acknowledge that our list of traits is not exhaustive and that the selected criteria for some traits could be contentious.

Prospective studies would benefit from additional paraclinical investigations to determine the prevalence of additional treatable traits, for example; ventilation heterogeneity and small airway disease. Finally, we

acknowledge that some traits may not be mutually exclusive and some maybe modified by asthma treatment. Associations between traits were not explored here, but have been discussed elsewhere (8).

In conclusion, the label-free, precision medicine approach provided by the treatable traits construct allowed for the identification of multiple treatment opportunities for patients with asthma, beyond the traditional step-wise approach. We eagerly await the results of prospective, longitudinal, clinical trials to determine whether this translates to improved clinical outcomes for individuals with respiratory disease.

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Statement of contribution:

AJS and SJF had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. IMA, RD, KFC and PJS defined the overall objectives and study design of U-BIOPRED project, and led the conduct of the study and delivery of the data used in this analysis. DES, LJF, GR, JHR, SB, ARS, ATB, IP, KS, PSB, MC, BD, S-ED, IH, NK, PM, TS, FS, SSW and SJF were involved in the study design and data collection. AJS and SJF wrote the initial draft of the manuscript. P-PH DES, LJF, GR, JHR, SB, ARS, ATB, IP, KS, PSB, MC, BD, S-ED, IH, NK, PM, TS, FS, IMA, SSW, RD, KFC and PJS were involved in reviewing the manuscript and providing feedback. All authors have seen and approved the final version of the manuscript.

Conflicts of interests:

Dr Simpson has nothing to disclose; Dr. Hekking has nothing to disclose; Dr Shaw reports advisory board fees from GSK, Novartis and AZ and travel fees from TEVA and AZ; Dr. Fleming reports personal fees from Vectura, personal fees from Novartis, personal fees from Boehringer Ingelheim, outside the submitted work; Dr. Roberts reports grants to University of Southampton during the conduct of the study; Dr. Riley reports he is employed by and hold shares in GlaxoSmithKline. Dr. Bates reports he is employed by and holds shares in GlaxoSmithKline. Dr. Sousa has nothing to disclose. Dr. Bansal has nothing to disclose. Dr. Pandis has nothing to disclose. Dr. Sun has nothing to disclose. Dr P Bakke has nothing to disclose. Dr. Caruso has nothing to disclose. Dr. B Dahlén reports personal fees from Advisory Board membership, personal fees from Payments for lectures, outside the submitted work; Dr. S-E Dahlén reports personal fees from AZ, GSK, Merck, Novartis, RSPR AB, Teva, outside the submitted work; Dr. Horvath reports personal fees from AstraZeneca, Boehringer-Ingelheim, GSK, Novartis, CSL Behring, Roche, Sandoz, Chiesi, Sager Pharma, Orion, Affidea and Teva, outside the submitted work. Dr. Krug reports grants from IMI, during the conduct of the study; Dr. Montuschi reports personal fees from AstraZeneca, outside the submitted work; Dr. Sandstrom reports personal fees from AstraZeneca, personal fees from GSK, personal fees from Boehringer Ingelheim, personal fees from Novartin, personal fees from Teva, outside the submitted work; Dr. Singer has nothing to disclose; Dr. Adcock reports grants from EU-IMI, during the conduct of the study; Dr. Wagers reports grants from Innovative Medicines Initiative, other from Roche, grants from European respiratory society, during the conduct of the study; other from GSK, other from European Respiratory Society, outside the submitted work; Dr. Chung reports personal fees from Advisory Board membership, grants for research, personal fees from payments for lectures, outside the submitted work; Dr. Sterk reports grants from Innovative Medicines Initiative (IMI), during the conduct of the study; Dr. Fowler has nothing to disclose.

Funding information:

The research leading to these results has received support from the Innovative Medicines Initiative (IMI) Joint Undertaking, under grant agreement no. 115010, resources for which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007–2013) and kind contributions from companies in the European Federation of Pharmaceutical Industries and Associations (EFPIA) (www.imi.europa.eu).

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Table 1. Treatable traits and defining criteria

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 AND/OR $FVC \geq 12\%$ AND ≥ 200 ml
	Type 2 inflammation	Sputum eosinophil count $\geq 2\%$ AND/OR blood eosinophils ≥ 450 cells per μl AND/OR FeNO > 50 ppb
	Neutrophilic inflammation	Sputum neutrophil count $> 60\%$
	Cough	Asthma Quality of Life Questionnaire (AQLQ) Question 12 score ≤ 4 AND/OR Sino-Nasal Outcomes Test (SNOT-20) Question score $4 \geq 3$
Extra-pulmonary	Exercise-induced respiratory symptoms	Medical history finding of "routine physical activity and/or physical exercise as asthma trigger"
	Bronchitis	Medical history finding of "Current AND/OR chronic bronchitis"
	Rhinosinusitis	Medical history finding of "Allergic/Non-allergic rhinitis active AND/OR 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 AND/OR 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

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.

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
Behavioural / Psychosocial	Underweight, n (%)	2/421 (1)	0/110 (0)	2/311 (1)	2/88(2)	P=0.399	P=0.175
	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

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