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Treatable traits in the NOVELTY study

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Abstract

Background and objective: Asthma and chronic obstructive pulmonary disease (COPD) are two prevalent and complex diseases that require personalized management. Although a strategy based on treatable traits (TTs) has been proposed, the prevalence and relationship of TTs to the diagnostic label and disease severity established by the attending physician in a real-world setting are unknown. We assessed how the presence/absence of specific TTs relate to the diagnosis and severity of 'asthma', 'COPD' or 'asthma + COPD'.

Methods: The authors selected 30 frequently occurring TTs from the NOVELTY study cohort (NOVEL observational longitudinal study; NCT02760329), a large ($n = 11,226$), global study that systematically collects data in a real-world setting, both in primary care clinics and specialized centres, for patients with 'asthma' ($n = 5932$, 52.8%), 'COPD' ($n = 3898$, 34.7%) or both ('asthma + COPD'; $n = 1396$, 12.4%).

Results: The results indicate that (1) the prevalence of the 30 TTs evaluated varied widely, with a mean \pm SD of 4.6 ± 2.6 , 5.4 ± 2.6 and 6.4 ± 2.8 TTs/patient in those with 'asthma', 'COPD' and 'asthma + COPD', respectively ($p < 0.0001$); (2) there were no large global geographical variations, but the prevalence of TTs was different in primary versus specialized clinics; (3) several TTs were specific to the diagnosis and severity of disease, but many were not; and (4) both the presence and absence of TTs formed a pattern that is recognized by clinicians to establish a diagnosis and grade its severity.

Conclusion: These results provide the largest and most granular characterization of TTs in patients with airway diseases in a real-world setting to date.

KEYWORDS

airways, allergy, asthma, bronchitis, chronic obstructive pulmonary disease, COPD, emphysema, smoking

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INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are two prevalent and heterogeneous chronic airway diseases that may overlap,^{1,2} thus requiring personalized clinical management.³ To this end, a strategy based on so-called treatable traits (TTs), which is agnostic to the traditional diagnostic labels of asthma or COPD, has been proposed.⁴⁻⁷ TTs can be identified by their observable clinical characteristics (i.e., phenotypes) and/or through validated biomarkers that indicate the presence/absence of distinct molecular mechanisms (i.e., endotypes) in the pulmonary (e.g., airflow limitation, chronic bronchitis, emphysema, among others), extra-pulmonary (e.g., obesity, cardiovascular disease or gastroesophageal reflux, among others) and behavioural/environmental domains (e.g., smoking, treatment compliance, familiar/social support among others).⁴⁻⁶ TTs can coexist, interact and change with time in the same patient.⁴⁻⁶ Recent clinical trials have shown that management of patients with chronic airway diseases guided by TTs improves clinical outcomes.⁷⁻¹³

TTs have been explored in several previous small studies in patients with asthma or COPD,⁷⁻¹⁴ but their prevalence and association with disease label and severity in a large, global, real-world setting that encompasses a broad spectrum of patients with chronic airway diseases are unknown. We hypothesized that the prevalence and association with disease label and severity vary by trait. We explored this hypothesis in the NOVELTY cohort (NCT02760329), a large, 3-year, real-world, prospective observational study in patients diagnosed with 'asthma', 'COPD' or 'asthma + COPD' in primary care and specialized centres around the globe.^{15,16}

METHODS

The methodology of NOVEL observational longitudinal study (NOVELTY) has been published elsewhere^{15,16} and is summarized briefly.

Study design and patients

NOVELTY is an ongoing prospective study that comprised patients diagnosed with 'asthma', 'COPD' or 'asthma + COPD' by their attending physician in primary care or pulmonary or allergy clinics from 19 countries in the Americas, Asia, Australia and Europe (first patient enrolled in July 2016).^{15,16} Patients were excluded only if their primary respiratory diagnosis was not asthma or COPD, they had either participated in a respiratory interventional trial during the previous 12 months or were considered unlikely to complete 3 years of follow-up. Data from patients in China and one site in Mexico were excluded from the present analysis due to new data transfer regulations and eligibility criteria, respectively. The severity of the disease (mild, moderate and

SUMMARY AT A GLANCE

This study shows which treatable traits are present and/or absent in patients diagnosed with 'asthma', 'COPD' (chronic obstructive pulmonary disease) and 'asthma + COPD' in a global, observational study of more than 11,000 patients (NOVELTY), and how their prevalence changes with disease severity.

severe) was established by the attending physicians based on their clinical judgement.¹⁶ Recruitment was stratified by diagnostic label and disease severity.

Measurements

Patients had yearly visits with follow-up data collected by their healthcare practitioner for 3 years or until study discontinuation, whichever comes first. Patients also completed questionnaires every 3 months using either a web-based platform or by telephone. As detailed elsewhere,¹⁵ demographics and clinical data were assessed using standardized questionnaires. Spirometry was determined following international recommendations and results were expressed as % predicted and proportion below the lower limit of normal using the Global Lung Function Initiative multi-ethnic reference equations.¹⁷ Peripheral venous blood was collected from consenting patients for cell counts.¹⁵ Thirty specific TTs (Table 1) were selected by co-authors based on previous literature, personal experience and availability in NOVELTY.

Statistical analysis

Differences across disease and severity levels were assessed using analysis of variance (followed by post hoc contrasts where necessary) or the chi-square test. Analyses were carried out using R version 3.5.1.²⁷ Because the very large sample of the study population greatly facilitated the finding of many *statistically* significant differences ($p < 0.05$) to identify *clinically* meaningful differences in prevalence, we used an arbitrary threshold of a ≥ 2 - or ≤ 0.5 -fold change difference. To identify associations between TTs, we computed their co-occurrence (i.e., the proportion of patients presenting two given TTs) per diagnostic label. The results of this co-occurrence are presented graphically in the form of a network analysis, where TT pairs co-occurring in $\geq 5\%$ of the individuals per diagnostic label are linked.²⁸ Finally, to investigate the association between TTs and diagnostic labels, TTs were dichotomized as binary variables (present/absent) and their associations with diagnostic labels were explored using chi-square tests.

TABLE 1 List and definitions of TTs used in this study

TT	Definition	References
Pulmonary		
Non-reversible airflow limitation	Post-bronchodilator FEV ₁ /FVC ratio <LLN	[4]
Bronchodilator reversibility	FEV ₁ reversibility ≥12% + ≥200 ml	[4]
PRISm	FEV ₁ <80% predicted + FEV ₁ /FVC ≥LLN	[18]
Frequent productive cough	SGRQ item 1 (cough) and item 2 (phlegm)	[4]
Non-EOS frequent productive cough	<100 blood eosinophils/μl + frequent productive cough	[19]
Exacerbation prone	≥1 Antibiotics and/or OCS-treated exacerbations in the last 12 months	[10,20]
Emphysema	Medical history + historical chest x-ray or chest CT or DLCO <LLN	[4]
Bronchiectasis	Medical history or historical chest CT	[6,21]
Obstructive sleep apnoea	Medical history	[4]
Nasal/sinus polyps	Medical history	[22]
Allergic rhinosinusitis	Medical history	[6]
Non-allergic rhinosinusitis	Medical history	[23]
Other respiratory allergies	Medical history (conjunctivitis or mould allergy or animal allergy)	[24]
Extra-pulmonary		
Non-respiratory allergies	Current/past total IgE or positive skin-prick (latex, drug, food), atopic eczema or anaphylaxis	[24]
Gastroesophageal reflux	Medical history	[5]
Obesity	BMI ≥30 kg/m ² or medical history (obesity) if BMI was missing	[6]
Cachexia	BMI <18.5 kg/m ²	[4]
Anaemia	Hb <130 g/L (men) or <110 g/L (women)	[6]
Osteoporosis	Medical history	[10]
Coronary heart disease	Medical history	[6]
Heart failure	Medical history	[6]
Cerebrovascular disease	Medical history	[25]
Depression or anxiety	Medical history	[4]
Systemic inflammation	Blood neutrophils ≥6 × 10 ⁹ /L	[10,26]
Th2 inflammation low	<100 blood eosinophils/μl + FeNO <20 ppb	Newly proposed
Th2 inflammation high	≥300 blood eosinophils/μl ± FeNO ≥50 ppb	[6]
Behavioural/environmental		
Smoking	Current smoker	[4]
Occupational exposures	Medical history	[4]
Indoor use of biomass/coal	Medical history	[4]
Frequent reliever use	Reliever used ≥3–6 times/week	Newly proposed

Abbreviations: CT, computed tomography; DLCO, diffusing capacity of the lungs for carbon monoxide; EOS, eosinophilic; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; LLN, lower limit of normal; OCS, oral corticosteroids; ppb, parts per billion; PRISm, preserved ratio impaired spirometry; SGRQ, St George's Respiratory Questionnaire; Th2, type-2 airway inflammation; TT, treatable trait.

RESULTS

Patient characteristics

The analysis included 11,226 patients, 5932 (52.8%) of whom were diagnosed with 'asthma', 3898 (34.7%) with 'COPD' and 1396 (12.4%) with 'asthma + COPD' (Table 2). Patients with 'asthma' were approximately a decade younger and included a higher proportion of females and never-smokers. Patients with 'COPD' or 'asthma + COPD' were more

symptomatic and reported a history of pneumonia more frequently than patients with asthma. Exacerbations were most frequently reported by patients with 'asthma + COPD'. Non-reversible airflow limitation was more prevalent and more severe in patients with 'COPD' or 'asthma + COPD' than in those with 'asthma'. Inhaled oral corticosteroids, leukotrienes and biologic treatments were used more frequently by patients with 'asthma' or 'asthma + COPD' than those with 'COPD'. Type-2 airway inflammation (Th2) biomarkers, such as circulating eosinophils and fractional

TABLE 2 Main characteristics (mean ± SD or %) of patients studied

Demographics and exposures	'Asthma' (n = 5932)	'Asthma + COPD' (n = 1396)	'COPD' (n = 3898)	p-value ^a
Age, mean, years ± SD	52.0 ± 17.1	64.7 ± 10.3	66.6 ± 9.6	<0.0001
Male, %	37.5	53.1	61.5	<0.0001
BMI, mean, kg/m ² ± SD	28.0 ± 6.6	28.5 ± 6.4	27.6 ± 6.3	<0.0001
Smoking status, %				<0.0001
Current smoker	8.1	24.5	29.6	
Former smoker	30.2	63.5	64.0	
Never smoked	61.7	12.0	6.3	
Cumulative smoking exposure, mean, pack-years ± SD	16.7 ± 23.3	36.5 ± 28.9	47.8 ± 40.2	<0.0001
Symptoms and clinical history				
Dyspnoea (mMRC ≥ Grade 2), %	20.8	43.6	53.2	<0.0001
Frequent productive cough, %	2.2	8.5	6.5	<0.0001
CAAT total score, mean ± SD	14.0 ± 8.5	17.2 ± 8.5	17.0 ± 8.3	<0.0001
SGRQ total score, mean ± SD	29.8 ± 20.9	39.9 ± 22.1	41.5 ± 21.8	<0.0001
Physician-reported exacerbations in the past 12 months, mean ± SD	0.7 ± 1.5	1.0 ± 1.8	0.6 ± 1.3	<0.0001
≥1 exacerbation, %	34.1	47.0	35.0	<0.0001
≥1 hospital admission, %	3.7	9.0	10.4	<0.0001
History of pneumonia, %	3.5	7.2	7.4	<0.0001
Lung function				
Post-bronchodilator FEV ₁ /FVC, mean ± SD	74.4 ± 11.8	59.6 ± 14.7	56.7 ± 16.2	<0.0001
Post-bronchodilator FEV ₁ /FVC <0.70, %	28.3	73.5	74.9	<0.0001
Post-bronchodilator FEV ₁ % predicted, mean ± SD	86.3 ± 20.3	68.3 ± 21.5	61.6 ± 23.0	<0.0001
Treatments				
Short-acting bronchodilator only (±add-on), %	8.5	10.8	23.2	<0.0001
Inhaled steroids maintenance, any combination, %	88.6	83.8	55.9	<0.0001
Triple therapy (ICS + LAMA + LABA), %	13.7	48.7	36.2	<0.0001
Leukotrienes or methylxanthine, %	30.7	26.4	9.2	<0.0001
Maintenance oral corticosteroids, %	3.9	3.9	1.9	<0.0001
Biologic treatment, %	9.8	4.2	0.1	<0.0001
Biomarkers				
Blood leucocytes ×10 ⁹ /L, mean ± SD	7.1 ± 2.1	7.6 ± 2.2	7.6 ± 2.1	<0.0001
Blood neutrophils ×10 ⁹ /L, mean ± SD	4.4 ± 1.8	4.9 ± 2.0	5.0 ± 1.9	<0.0001
Blood lymphocytes ×10 ⁹ /L, mean ± SD	2.0 ± 0.6	2.0 ± 0.7	2.0 ± 0.7	0.8206
Blood eosinophils/μl, mean ± SD	222.8 ± 189.8	212.4 ± 179.2	182.9 ± 127.1	<0.0001
Platelets ×10 ⁹ /L, mean ± SD	261.4 ± 72.4	264.6 ± 78.9	250.3 ± 80.2	<0.0001
FeNO, ppb, mean ± SD	32.3 ± 30.7	24.1 ± 23.8	19.9 ± 17.9	<0.0001
Th2, %				<0.0001
Low	10.1	14.1	15.0	
Medium	57.4	60.0	67.4	
High	32.5	25.9	17.6	

Abbreviations: ANOVA, analysis of variance; CAAT, Chronic Airways Assessment Test; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting β₂-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council; ppb, parts per billion; SGRQ, St George's Respiratory Questionnaire; Th2, type-2 airway inflammation; Th2-high, ≥300 blood eosinophils/μl ± FeNO ≥50 ppb; Th2-low, <100 blood eosinophils/μl + FeNO <20 ppb; Th2-medium, neither Th2-low nor Th2-high.

^ap-values are based on the chi-square test for categorical variables and ANOVA for continuous variables.

exhaled nitric oxide, were higher in patients with 'asthma' and lower in patients with 'COPD'. However, differences in eosinophil levels were of small magnitude and likely statistically significant due to the large sample size. Patients with

COPD showed higher levels of circulating leucocytes and neutrophils. Figure S1 in the Supporting Information shows the distribution of disease severity across disease labels. Although there were statistically significant differences, these

FIGURE 1 Prevalence of the investigated TTs in the entire study population (A) and by geographical region (B). Non-evaluable traits due to missing data were adjusted by weighting for the proportion of positive traits among those evaluable in a patient. EOS, eosinophilic; PRISm, preserved ratio impaired spirometry; Th2, type-2 airway inflammation; TT, treatable trait

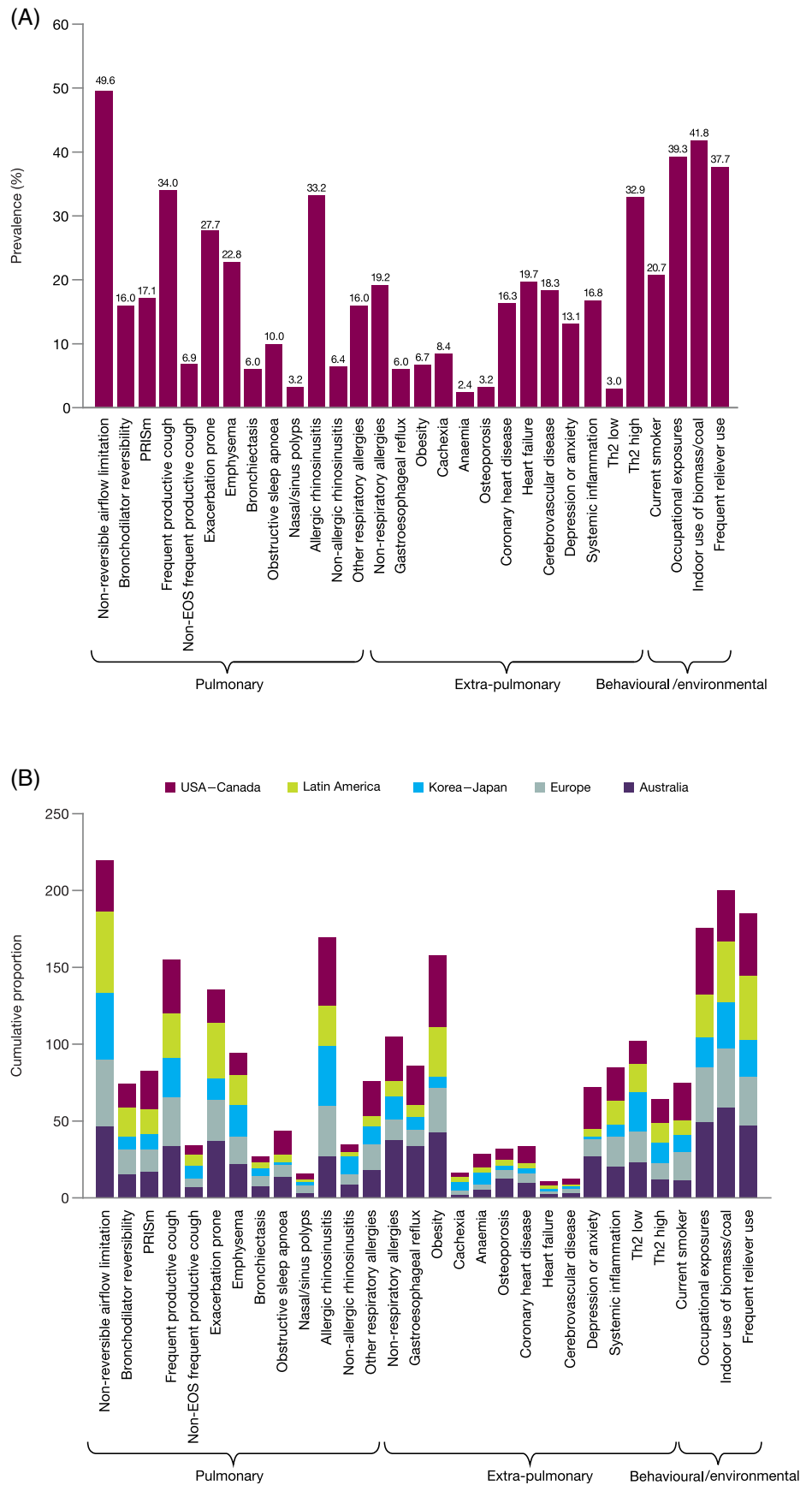


TABLE 3 Prevalence of the 30 analyzed TTs in patients with 'asthma', 'asthma + COPD' or 'COPD'

	'Asthma'	'Asthma + COPD'	'COPD'	p-value
Pulmonary				
Non-reversible airflow limitation	23.2	61.8	63.9	<0.0001
Bronchodilator reversibility	15.8	19.1	13.1	<0.0001
PRISm	15.6	17.0	18.8	0.0008
Frequent productive cough	25.0	38.9	38.1	<0.0001
Non-EOS frequent productive cough	4.6	8.8	7.4	0.0002
Exacerbation prone	24.0	35.1	24.1	<0.0001
Emphysema	1.7	29.2	37.6	<0.0001
Bronchiectasis	4.7	7.7	5.7	<0.0001
Obstructive sleep apnoea	7.7	11.7	10.7	<0.0001
Nasal/sinus polyps	5.6	3.2	0.8	<0.0001
Allergic rhinosinusitis	51.5	36.3	11.9	<0.0001
Non-allergic rhinosinusitis	8.6	8.0	2.6	<0.0001
Other respiratory allergies	24.8	19.2	3.9	<0.0001
Extra-pulmonary				
Non-respiratory allergies	22.1	21.6	13.9	<0.0001
Gastroesophageal reflux	14.5	20.4	15.5	<0.0001
Obesity	31.9	35.7	31.2	0.0085
Cachexia	2.6	2.4	4.2	<0.0001
Anaemia	3.1	7.8	7.3	<0.0001
Osteoporosis	4.9	8.9	6.3	<0.0001
Coronary heart disease	2.8	9.9	12.5	<0.0001
Heart failure	0.6	2.5	4.2	<0.0001
Cerebrovascular disease	1.6	4.2	3.7	<0.0001
Depression or anxiety	13.1	20.5	15.4	<0.0001
Systemic inflammation	15.0	21.5	22.7	<0.0001
Th2-low	10.1	14.1	15.0	<0.0001
Th2-high	24.2	18.7	11.9	<0.0001
Behavioural/environmental				
Current smoker	8.1	24.5	29.6	<0.0001
Occupational exposures	29.2	45.3	43.3	<0.0001
Indoor use of biomass/coal	30.7	51.8	42.9	<0.0001
Frequent reliever use	30.5	45.6	37.1	<0.0001

Note: Data show percentage of patients with available data.

Abbreviations: COPD, chronic obstructive pulmonary disease; EOS, eosinophilic; PRISm, preserved ratio impaired spirometry; Th2, type-2 airway inflammation; TT, treatable trait.

are likely the result of recruiting a large number of patients, but this large population of mild, moderate and severe disease in turn allowed the investigation of TTs in the different severity strata.

Prevalence of TTs in the entire study population

The prevalence of the 30 TTs studied here: (1) varied from almost 50% (non-reversible airflow limitation) to <10% in several other TTs (Figure 1A); (2) did not change substantially after adjusting for age (Table S1 in the Supporting Information); (3) was different in patients diagnosed in

primary versus specialized care clinics (Table S2 in the Supporting Information); (4) the mean number of TTs per patient was 5.1 ± 2.7 , indicating that most TTs do not present in isolation; (5) although there were many statistically significant regional differences in the prevalence of TTs (Tables S3–S5 in the Supporting Information), the TT distribution pattern was similar in United States–Canada, Latin America, Korea–Japan, Europe and Australia (Figure 1B); and (6) the presence (OR > 1) or absence (OR < 1) of 20 (66.6%) TTs was significantly associated with severe disease (p -values: 0.05 to $<10^{140}$ as indicated by the edge thickness), whereas the remaining 10 (33.4%) TTs were not (Figure S2 in the Supporting Information).

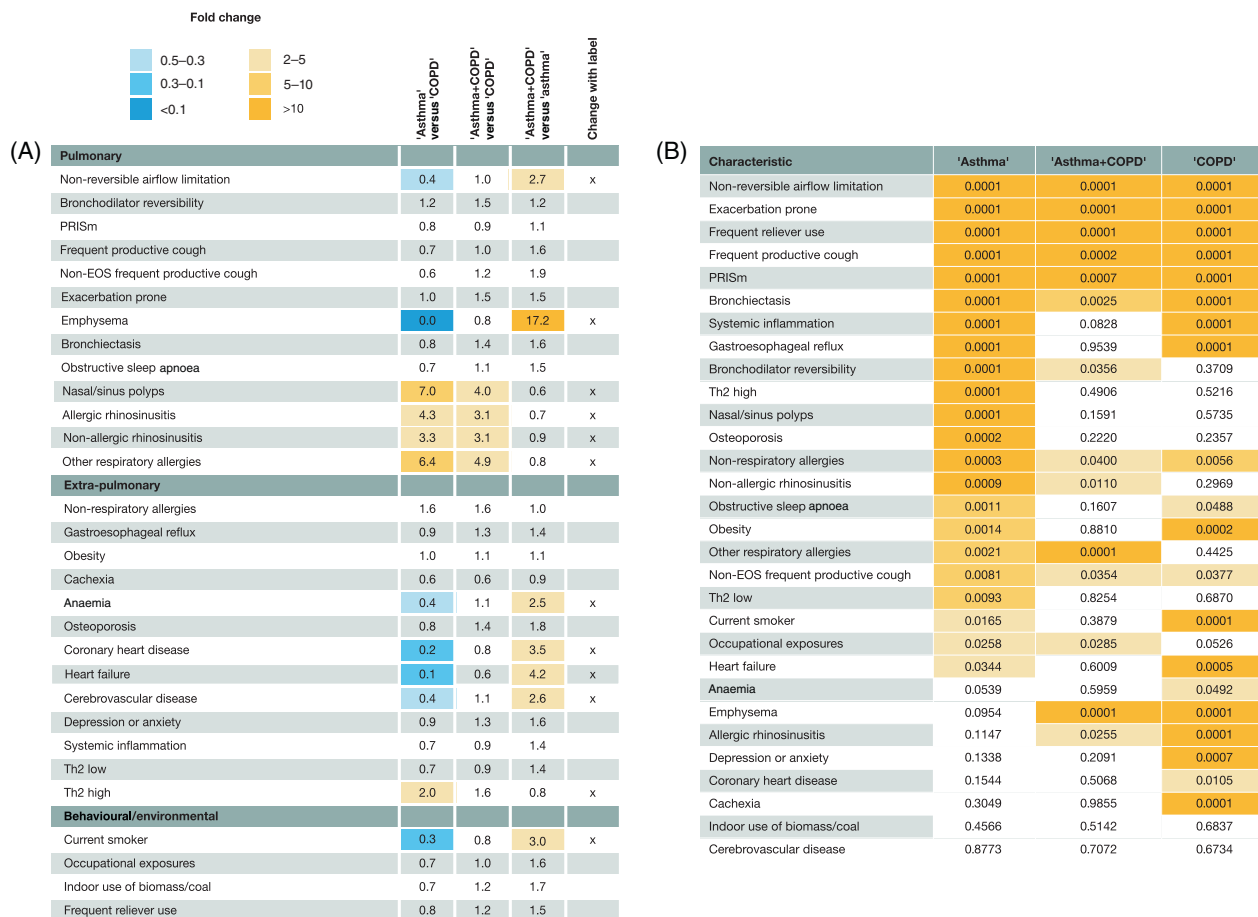


FIGURE 2 (A) Heat map of fold changes in prevalence of TTs across the three diagnostic labels considered (columns from left to right: 'asthma' vs. 'COPD', 'asthma + COPD' vs. 'COPD' and 'asthma + COPD' vs. 'asthma'). The final column highlights (x) those TTs with a ≥ 2 - (orange cells) or ≤ 0.5 - (blue cells) fold change between diagnostic labels. (B) Heat map of statistically significant p -values (ANOVA) associated with differences in prevalence of a given TT by disease severity in patients with 'asthma', 'asthma + COPD' and 'COPD'. TTs are ordered by p -value in patients with 'asthma'. Darkest shading, $p \leq 0.001$; mid-shading, $p \leq 0.01$; light shading, $p \leq 0.05$; no shading, $p > 0.05$. ANOVA, analysis of variance; COPD, chronic obstructive pulmonary disease; EOS, eosinophilic; PRISm, preserved ratio impaired spirometry; Th2, type-2 airway inflammation; TT, treatable trait

Relationship of TTs with diagnostic label

Differences in the prevalence of specific TTs across diagnostic labels achieved statistical significance in all 30 TTs (Table 3), likely due to the large sample size of the studied population. To address this, Figure 2A presents a fold change-based heat map for the three potential comparisons across the three diagnostic labels. It shows that the prevalence of 12 (40%) TTs changed with disease label. Furthermore, the pattern of TTs in patients with 'asthma' was opposite in patients with 'COPD', with a mixed pattern in those with 'asthma + COPD'. As these particular TTs are used in clinical practice to establish these diagnoses, we labelled them as 'diagnostic TTs'. Importantly, however, the prevalence of the remaining 18 (60%) TTs was similar across disease labels, including some highly clinically relevant TTs such as bronchodilator reversibility, frequent productive cough and exacerbation prone (Figure 2A). Figure S3 in the Supporting Information shows that, on average, patients with 'asthma' had

the lowest number of TTs (4.6 ± 2.6), followed by those with 'COPD' (5.4 ± 2.6) and those with 'asthma + COPD' (6.4 ± 2.8 ; all $p < 0.0001$).

Relationship of TTs with disease severity

The presence (OR > 1) or absence (OR < 1) of 20 (66.6%) TTs was significantly associated with severe disease (p -values: 0.05 to $< 10^{-140}$; Figure S2 in the Supporting Information). However, these associations varied by disease label (Table S6 in the Supporting Information). Figure 2B shows a heat map of the TT where prevalence significantly varied by disease severity within each disease label. The number (and type) of TTs where prevalence changed significantly in relation to disease severity was higher in 'asthma' than in 'COPD' or 'asthma + COPD'. In contrast, the prevalence of non-reversible airflow limitation, exacerbation prone, frequent reliever use, preserved ratio impaired spirometry and bronchiectasis was significantly related, with higher disease

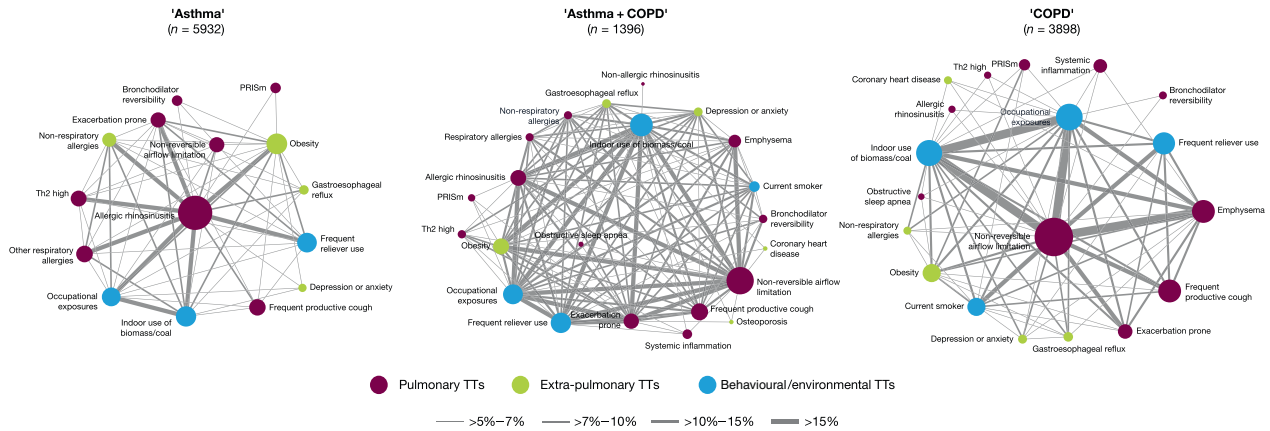


FIGURE 3 Network of TT co-occurrence (i.e., the proportion of patients presenting two given TTs) by disease label. Colour node indicates their pulmonary, extra-pulmonary or behavioural/environmental origin. Node size is proportional to its prevalence, and the width of the edge (links) indicates the proportion of patients in whom a given TT pair co-occur. COPD, chronic obstructive pulmonary disease; PRISm, preserved ratio impaired spirometry; Th2, type-2 airway inflammation; TT, treatable trait

	'Asthma'	'Asthma+COPD'	'COPD'	Severe 'asthma'	Severe 'asthma+COPD'	Severe 'COPD'
Non-reversible airflow limitation	0.3	2.1	4.5	2.7	4.0	6.2
Bronchodilator reversibility	1.3	1.5		1.9	1.8	
PRISm				1.4		0.4
Frequent productive cough	0.7	1.4	1.8	1.9	1.9	1.4
Non-EOS frequent productive cough	0.7	1.5	1.9	1.9	2.2	1.6
Exacerbation prone	1.1	1.7	1.3	3.2	2.9	2.6
Emphysema	0.2	1.8	25.0		2.7	2.7
Bronchiectasis	1.4	1.3		2.5	2.0	1.5
Obstructive sleep apnoea				1.3	1.4	
Nasal/sinus polyps	7.8		0.2	1.9		0.4
Allergic rhinosinusitis	5.1	1.4	0.3		1.6	0.6
Cerebrovascular disease		1.4	1.6			
Respiratory allergies	5.7	1.7	0.4	1.4	2.2	0.8
Depression or anxiety	0.8	1.7	1.7		1.4	0.7
Gastroesophageal reflux	1.2	1.4		1.4	1.3	0.6
Obesity		1.2		1.2		0.7
Cachexia	0.4		2.9			2.7
Anaemia		1.5	1.6	1.6	1.6	0.7
Osteoporosis		1.5		1.4	1.5	
Coronary heart disease	0.6		2.4			
Heart failure	0.4		3.7	1.9		1.5
Systemic inflammation	0.7		1.7	2.2	1.5	1.8
Th2 low	0.6		1.8			
Th2 high	2.3		0.5	1.4		
Current smoker	0.2	1.8	10.5	0.8	1.5	0.7
Occupational exposures	0.8	1.4	1.5	1.2	1.7	1.2
Indoor use of biomass/coal		1.6	1.3		1.5	
Frequent reliever use	0.9	1.7	1.5	2.5	3.1	2.2
Non-allergic rhinosinusitis	3.7	1.4	0.4	1.3		0.5
Non-respiratory allergies	1.6	1.3	0.8	1.3	1.5	0.8

FIGURE 4 Pattern recognition heat map in relation to diagnostic label (left three columns) and severity assessment (right three columns). For this analysis, TTs were dichotomized as binary variables (present/absent) and their associations with diagnostic labels and severity of disease were explored using chi-square tests. Coloured cells indicate statistically significant associations ($p < 0.05$), where cell colour (orange or blue) corresponds to an OR > 1 (i.e., presence of the TT) or an OR < 1 (i.e., absence of the TT), respectively. COPD, chronic obstructive pulmonary disease; EOS, eosinophilic; PRISm, preserved ratio impaired spirometry; Th2, type-2 airway inflammation; TT, treatable trait

severity in all three diseases; the prevalence of other TTs was independent of the level of disease severity.

TT co-occurrence

Figure 3 presents a network of TT co-occurrence by disease label. In 'asthma', the most frequent TT pairs included rhinosinusitis, respiratory and non-respiratory allergies, Th2-high markers, obesity, occupational exposures, indoor use of biomass/coal and frequent reliever use. In 'COPD', the most prevalent TT pairs included non-reversible airflow limitation, emphysema, frequent productive cough, environmental exposures (including smoking), exacerbation prone and frequent reliever use (Figure 3). Finally, the co-occurrence network was most complex in patients diagnosed with 'asthma + COPD' (albeit slightly weaker, where seven TTs were involved in more than seven highly prevalent TT pairs, including allergic rhinosinusitis [as in the 'asthma' network], some TTs with high connectivity in the 'COPD' network [such as airflow limitation and occupational exposures], as well as exacerbation prone and obesity that also emerged in the 'asthma + COPD' network). Importantly, this co-occurrence analysis sought to describe relationships between TTs, not to infer causal associations.

Pattern recognition

In clinical practice, physicians establish a given diagnosis by pattern recognition (i.e., by identifying a number of present and absent traits).²⁹ Figure 4 shows that 'asthma' was significantly associated with the presence of 10 TTs and the absence of 13 other TTs, 'COPD' with the presence of 17 other TTs and the absence of six TTs and 'asthma + COPD' with the presence of 21 TTs (which included most of those already identified in patients diagnosed with 'asthma' or 'COPD') but with no absent TTs. Figure 4 also shows that the TT pattern changes in relation to disease severity, but in opposite directions in severe 'asthma' and severe 'COPD' as the former was characterized by an increase in the number of present TTs and a reduction in absent TTs, whereas the opposite occurred in 'COPD'. By contrast, the pattern of severe 'asthma + COPD' did not change substantially with disease severity, except for the consideration of systemic inflammation and the non-association with cerebrovascular disease, obesity and non-allergic rhinosinusitis.

DISCUSSION

This study shows that: (1) the prevalence of the 30 TTs investigated here varies widely within the NOVELTY cohort, without clear geographical variations, but differs by care setting; (2) six (pulmonary) TTs were significantly associated with a diagnosis of 'asthma' or 'COPD' ('diagnostic TTs'), but the prevalence of the remaining pulmonary, and most of

the extra-pulmonary and behavioural/environmental TTs was independent of the disease label; (3) the diagnosis of 'asthma + COPD' was associated with all TTs identified in 'asthma' or 'COPD' separately; (4) some, but not all, TTs can co-occur and their prevalence varies with disease severity; (5) the pattern of present/absent TTs relates to disease label and severity assessment. Collectively, these results provide a comprehensive repository of information on TTs in chronic airway diseases, contribute to better delineate their heterogeneity and help to better understand how the presence/absence of different TTs contribute to a specific diagnostic label and the assessment of disease severity by the attending physician.

Several previous smaller studies have investigated TTs in patients with asthma, COPD or both.^{8–14} An analysis of data at recruitment in the NOVELTY cohort demonstrated marked heterogeneity within, and considerable overlap between, physician-assigned diagnoses and the assessment of severity in patients with 'asthma' and/or 'COPD'.¹⁶ The current analysis of TTs is the largest to date and the first to compare their prevalence, relationship with the diagnostic label, disease severity and pattern of co-occurrence in different real-life healthcare settings.

In this study we identified six *pulmonary* TTs, including nasal sinus polyps and several allergies in 'asthma' and non-reversible airflow limitation and emphysema in 'COPD' (plus smoking and comorbidities), that were distinctly associated with the diagnostic labels of 'asthma' or 'COPD'. This is not surprising as these *pulmonary* 'diagnostic TTs' are most often used in practice to precisely establish these clinical diagnoses. However, importantly for clinical practice, the prevalence of 18 pulmonary, extra-pulmonary and/or behavioural/environmental TTs was similar, irrespective of the diagnostic label used, including some TTs traditionally considered almost exclusive to 'asthma' or 'COPD', such as bronchodilator reversibility, Th2 and frequent productive cough. This has clinical relevance because it indicates a high degree of heterogeneity, and that these 18 TTs should be considered in any patient with chronic airway disease, irrespective of the diagnostic label.

We also found that the prevalence of some, but not all, TTs increased with disease severity and that the number of TTs typically associated with a perception of a more severe disease varied between disease labels, whereas the prevalence of other TTs did not change at all. This suggests that the individual consideration of TTs, irrespective of label and severity assessment, can facilitate more personalized and precise management and, eventually, a better outcome. Moreover, we also found that a given clinical label was significantly associated with a pattern of both present and absent TTs (Figures 3 and 4), in keeping with the concept that, in clinical practice, physicians establish a diagnosis (and start a treatment) based on pattern recognition;²⁹ when a precise clinical diagnosis of 'asthma' or 'COPD' is difficult, 'asthma + COPD' appears to be chosen instead.

Our study has several strengths and limitations. The large sample size, global participation and real-world setting, which allowed for the inclusion of patients with

chronic airway diseases who are typically excluded from randomized clinical trials,^{30–33} are strengths. Indeed, the generalizability of NOVELTY data has been presented previously.¹⁶ However, we acknowledge several potential limitations. First, we studied 30 TTs selected by co-authors based on previous literature, personal experience and availability in the NOVELTY database (Table 1); yet the list of potential TTs of interest is much larger^{4–7} and other TTs may need to be considered in future studies. In particular, some potentially relevant TTs in the behavioural/environmental domain, such as adherence, inhaler technique and/or inhaler polypharmacy, were not included in NOVELTY¹⁵ and could not, therefore, be analyzed here. Second, the diagnostic label and assessment of disease severity were established in each patient by the attending physician, according to their own clinical experience and judgement¹⁶ and possibly, but not certainly, according to the current guideline recommendations. Although, at first glance, this may be seen as a limitation, we think that it actually allows for a better understanding of what drives disease labelling and severity scoring (hence, likely treatment too) by the attending physician in real-world clinical practice.¹⁶ Accordingly, the higher number of TTs in patients recruited in specialty clinics can imply either a better diagnostic and therapeutic workup or a greater disease complexity. In addition, the lack of mandatory computed tomography scans for the identification of specific TTs (e.g., emphysema, bronchiectasis or other comorbid conditions) and differences in the definitions used versus those proposed in clinical trials^{34–36} may lead to an inaccurate (underestimation) of the true prevalence of these conditions. Finally, the cross-sectional nature of this analysis does not allow for the investigation of the stability of TTs over time, their relationship with specific therapeutic interventions and/or with relevant clinical outcomes.

In conclusion, this analysis provides the largest and most granular characterization of TTs in patients with airway diseases in a real-world setting to date. It shows that a few TTs are tightly linked with the disease label of ‘asthma’ (allergic and non-allergic rhinosinusitis, nasal sinus polyps and several allergies) or ‘COPD’ (non-reversible airflow limitation and emphysema), whereas many others occur independent of the diagnostic label. Likewise, the prevalence of some, but not all, TTs changes with the assessment of disease severity by the attending physician.

AUTHOR CONTRIBUTION

Alvar Agustí: Conceptualization (equal); formal analysis (equal); investigation (equal); methodology (equal); writing – original draft (lead); writing – review and editing (equal). **Eleni Rapsomaniki:** Conceptualization (equal); formal analysis (equal); investigation (equal); methodology (equal); writing – review and editing (equal). **Richard Beasley:** Conceptualization (equal); formal analysis (equal); investigation (equal); methodology (equal); writing – review and editing (equal). **Rod Hughes:** Conceptualization (equal); formal analysis (equal); investigation (equal); methodology

(equal); writing – review and editing (equal). **Hana Müllerová:** Conceptualization (equal); formal analysis (equal); investigation (equal); methodology (equal); writing – review and editing (equal). **Alberto Papi:** Conceptualization (equal); formal analysis (equal); investigation (equal); methodology (equal); writing – review and editing (equal). **Ian D. Pavord:** Conceptualization (equal); formal analysis (equal); investigation (equal); methodology (equal); writing – review and editing (equal). **Maarten van den Berge:** Conceptualization (equal); formal analysis (equal); investigation (equal); methodology (equal); writing – review and editing (equal). **Rosa Faner:** Conceptualization (equal); formal analysis (equal); investigation (equal); methodology (equal); writing – original draft (lead); writing – review and editing (equal).

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A list of collaborators (NOVELTY Study Investigators) is available in Appendix S1 in the Supporting Information.

CONFLICTS OF INTEREST

Alvar Agustí has received payments in his role as a member of the scientific committee of NOVELTY; received research grants from AstraZeneca, Chiesi, GSK, Menarini, MSD and Zambon; consulting fees from AstraZeneca, Chiesi, GSK, Menarini, MSD and Zambon; and payment or honoraria from AstraZeneca, Chiesi, GSK, Menarini, MSD and Zambon. Eleni Rapsomaniki and Rod Hughes are employees of AstraZeneca. Hana Müllerová is an employee and shareholder of AstraZeneca. Richard Beasley received research grants from AstraZeneca, Cure Kids (NZ), Genentech, GSK and HRC (NZ); consulting fees from AstraZeneca, Avillion and Theravance; payment or honoraria from AstraZeneca, Cipla and Asthma and Respiratory Foundation NZ; support for attending meetings from AstraZeneca and Theravance; and is the Chair of the adult asthma guidelines group for the Asthma and Respiratory Foundation of NZ. Alberto Papi received research grants from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Pfizer, Sanofi and Teva; consulting fees from AstraZeneca, Avillion, Chiesi, Elpen Pharmaceuticals, GSK, IQVIA, Novartis and Sanofi; and payment or honoraria from AstraZeneca, Avillion, Boehringer Ingelheim, Chiesi, Edmond Pharma, Elpen Pharmaceuticals, GSK, IQVIA, Menarini, MSD, Mundipharma, Novartis, Sanofi, Teva and Zambon. Ian D. Pavord received research grants from Chiesi; consulting fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Dey Pharma, Genentech, GSK, Knopp Biosciences, Merck, MSD, Napp Pharmaceuticals, Novartis, Regeneron Pharmaceuticals Inc.,

Respivert, Schering-Plough and Teva; payment or honoraria from Aerocrine, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Regeneron Pharmaceuticals Inc., Sanofi and Teva; support for attending meetings from AstraZeneca, Chiesi, GSK, Regeneron Pharmaceuticals Inc., Sanofi, Teva and Napp Pharmaceuticals; and other financial or non-financial interests from AstraZeneca, Boehringer Ingelheim, GSK, Regeneron Pharmaceuticals Inc., Sanofi and Teva. Maarten van den Berge received research grants from Genentech, GSK, Novartis, Roche and Sanofi. Rosa Faner received research grants from AstraZeneca, GSK, Instituto de Salud Carlos III—Spanish National Health Service and Menarini; consulting fees from GSK; and payment or honoraria from Chiesi.

DATA AVAILABILITY STATEMENT

This manuscript has associated data in a repository. Data underlying the findings described in this manuscript, including individual de-identified participant data, protocols and clinical trial documents, may be obtained in accordance with AstraZeneca's data-sharing policy (described at <https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure>) through Vivli (<https://vivli.org/>).

HUMAN ETHICS APPROVAL DECLARATION

The study was approved by the relevant Institutional Review Boards, and all patients provided written informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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