Heterogeneity within and between physician-diagnosed asthma and/or COPD: NOVELTY cohort

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Shareable abstract (@ERSpublications)
Heterogeneity within and between physician-diagnosed asthma and/or COPD in the NOVELTY cohort at baseline suggests that current diagnostic and severity classifications poorly differentiate between clinically important phenotypes https://bit.ly/3qc4kNC

Cite this article as: Reddel HK, Vestbo J, Agustí A, *et al*. Heterogeneity within and between physician-diagnosed asthma and/or COPD: NOVELTY cohort. *Eur Respir J* 2021; 58: 2003927 [DOI: 10.1183/13993003.03927-2020].

This article has supplementary material available from erj.ersjournals.com

This article has an editorial commentary: https://doi.org/10.1183/13993003.00627-2021

Received: 27 Oct 2020
Accepted: 8 Feb 2021

Abstract

Background Studies of asthma and chronic obstructive pulmonary disease (COPD) typically focus on these diagnoses separately, limiting understanding of disease mechanisms and treatment options. NOVELTY is a global, 3-year, prospective observational study of patients with asthma and/or COPD from real-world clinical practice. We investigated heterogeneity and overlap by diagnosis and severity in this cohort.

Methods Patients with physician-assigned asthma, COPD or both (asthma+COPD) were enrolled, and stratified by diagnosis and severity. Baseline characteristics were reported descriptively by physician-assigned diagnosis and/or severity. Factors associated with physician-assessed severity were evaluated using ordinal logistic regression analysis.

Results Of 11 243 patients, 5940 (52.8%) had physician-assigned asthma, 1396 (12.4%) had asthma +COPD and 3907 (34.8%) had COPD; almost half were from primary care. Symptoms, health-related quality of life and spirometry showed substantial heterogeneity and overlap between asthma, asthma +COPD and COPD, with 23%, 62% and 64% of patients, respectively, having a ratio of post-bronchodilator forced expiratory volume in 1 s to forced vital capacity below the lower limit of normal. Symptoms and exacerbations increased with greater physician-assessed severity and were higher in asthma+COPD. However, 24.3% with mild asthma and 20.4% with mild COPD had experienced ⩾1 exacerbation in the past 12 months. Medication records suggested both under-treatment and over-treatment relative to severity. Blood eosinophil counts varied little across diagnosis and severity groups, but blood neutrophil counts increased with severity across all diagnoses.

Conclusion This analysis demonstrates marked heterogeneity within, and overlap between, physician-assigned diagnosis and severity groups in patients with asthma and/or COPD. Current diagnostic and severity classifications in clinical practice poorly differentiate between clinical phenotypes that may have specific risks and treatment implications.

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are among the most common non-communicable diseases worldwide, contributing a significant burden to patients and healthcare systems [1]. There is increasing recognition that there are numerous phenotypes of asthma and COPD, and that conventional diagnostic criteria for the two diseases overlap [2, 3]. Despite this, most mechanistic studies and regulatory clinical trials are limited to either asthma or COPD based on conventional diagnostic criteria, and may exclude up to 90% of real-world patients [4, 5]. This has hampered progress in understanding the pathobiology of obstructive lung disease and its relevance to patients in clinical practice. Observational studies and pragmatic trials with broader eligibility criteria are needed to complement the randomised controlled trial evidence base [6].

To support the development of personalised management and improve clinical outcomes, the 2018 Asthma Lancet Commission [7] called for new ways of classifying asthma and COPD based on clinical or inflammatory characteristics (phenotypes) and underlying mechanisms. Advances in developing effective treatments require identification of precise molecular mechanisms or distinct treatment responses that can be linked to well-defined patient subgroups (*i.e.* endotypes) [8].

Although important insights have been obtained from studying selected or geographically limited populations with a single diagnostic label ("asthma" or "COPD") based on conventional diagnostic criteria [9–11], there have been few prospective studies in real-world clinical practice that have included patients with asthma and/or COPD.

The NOVEL observational longiTudinal studY (NOVELTY) [12] is a global, 3-year, prospective observational study across the full spectrum of asthma and/or COPD (www.clinicaltrials.gov, NCT02760329). The primary objectives of NOVELTY are to describe patient characteristics, treatment patterns and disease burden over time, and to identify clinical phenotypes and molecular endotypes associated with differential outcomes in patients with a diagnosis or suspected diagnosis of asthma and/or COPD [12]. NOVELTY is systematically collecting real-world data from specialist centres and primary care, including many patients who would usually be excluded from studies in "pure" asthma or COPD.

Here, we investigate heterogeneity among, and overlap between, groups identified by physician-assigned diagnosis and severity labels among patients being treated for asthma and/or COPD in the community, and we describe the baseline clinical, physiological and biomarker characteristics of the global NOVELTY population.

Methods

Study design

The NOVELTY study design has been published previously [12] and details can also be found on the study website (noveltystudy.com). Briefly, patients aged ⩾18 years with a physician-assigned diagnosis or suspected (*i.e.* not confirmed) diagnosis of asthma, COPD or both (asthma+COPD) were enrolled by primary care physicians, pulmonologists or allergists from active clinical practices in 19 countries in the Americas, Asia, Australia and Europe; 11 countries also recruited patients ⩾12–<18 years of age (supplementary table S1). Patients were excluded only if their primary respiratory diagnosis was not asthma or COPD, they had participated in a respiratory interventional trial during the previous 12 months or they were considered unlikely to complete 3 years of follow-up. To ensure sufficient numbers for regional or subgroup analyses, sampling was stratified by diagnosis (asthma, asthma+COPD, COPD) and by physician-assessed severity (mild, moderate, severe); enrolment was capped in some subgroups in some countries when target numbers were reached. No diagnostic or severity criteria were provided.

The study was approved in each participating country by the relevant institutional review boards and all patients provided written informed consent.

Measurements

As detailed elsewhere [12], physicians recorded baseline demographics; smoking status; disease history (years since diagnosis, age of onset); respiratory and non-respiratory comorbidities; diagnosis of emphysema; allergies (including whether confirmed by allergy testing); medications; fractional exhaled

nitric oxide (F_{ENO}) level (supplementary material); and pre- and post-bronchodilator forced expiratory volume in 1 s (FEV_1), bronchodilator responsiveness (reversibility), forced vital capacity (FVC), FEV_1/FVC and forced expiratory flow at 25–75% of FVC ($FEF_{25–75\%}$), with predicted and lower limit of normal (LLN) values based on Global Lung Function Initiative multi-ethnic reference equations [13]. Physicians were asked to record exacerbations as: "During the past 12 months, on how many occasions has your patient experienced an exacerbation of their asthma or COPD beyond the patient's usual day-to-day variance?" [14]. For bronchodilator responsiveness testing, patients were required to have withheld short-acting bronchodilators for ⩾6 h and long-acting bronchodilators for 12–24 h, as appropriate. Baseline data for selected patient-reported outcomes (PROs) that are "diagnosis-agnostic" (*i.e.* not specific to asthma or COPD) for evaluating symptoms (modified Medical Research Council (mMRC) dyspnoea grade) [15] and health-related quality of life (HRQoL) or health status (St George's Respiratory Questionnaire (SGRQ) total score [16] and Chronic Airways Assessment Test (CAAT) score) are also reported. The CAAT (© 2009 GlaxoSmithKline; all rights reserved) is a modified (with permission) version of the COPD Assessment Test [17], with the term "COPD" replaced with "chronic airways" and "pulmonary disease" in the questionnaire title and instruction, respectively [12]. Physicians did not have access to PRO scores when assessing asthma and COPD severity. Blood was collected from consenting patients for cell counts.

Statistical analysis

Results are presented as descriptive statistics, stratified by physician-assigned diagnosis/suspected diagnosis (combined), physician-assessed severity (mild, moderate, severe/very severe (pooled)), recruitment setting (primary care or non-primary care) and/or diagnosis or suspected diagnosis. Medications were analysed by class (supplementary table S2). Data for patients from China were excluded from the present analyses owing to a change in regulations about data transfer in May 2019.

Factors independently associated with physician-assessed severity were evaluated using ordinal logistic regression analysis, treating severity categorisation as an ordinal variable. The variables included in the ordinal models were selected using stepwise regression, starting with a non-redundant set of variables (supplementary material). Ordinal regression models were fitted for asthma-only patients and COPD-only patients separately, and overall. Proportional odds ratios and 95% confidence intervals are reported. All analyses were performed using R version 5.1.2 (R Foundation for Statistical Computing).

Results

Analysis population

This analysis includes all patients from 18 countries (excluding China) who met the inclusion criteria and had data for diagnosis as of March 5, 2018 (N=11 243; supplementary table S1).

Patients were enrolled from primary care (46.7%), university hospitals (26.7%), specialist research facilities (11.8%), non-university hospitals (8.7%), specialist clinics (4.4%) and unknown settings (0.9%). Patients recruited from primary care had milder asthma and were less likely to have a diagnosis of emphysema or to have had allergy testing or post-bronchodilator spirometry performed than those recruited from other settings (supplementary table S3).

Heterogeneity and overlap by physician-assigned diagnosis

At baseline, 5940 patients (52.8%) had a physician-assigned diagnosis of asthma only, 1396 (12.4%) asthma+COPD and 3907 (34.8%) COPD only (table 1); the diagnosis was recorded as suspected for 4.3% (supplementary table S4). Overall, 52.3% were female (asthma 62.5%, COPD 38.5%). Patients with asthma were younger than those with asthma+COPD or COPD.

On average, patients with asthma had been diagnosed earlier than those with asthma+COPD or COPD (table 1). Respiratory symptoms reportedly commenced before 12 years of age for 25.0% and 21.0% of asthma and asthma+COPD patients, respectively, but also for 4.5% of COPD patients (table 1). Among patients with asthma+COPD, the first diagnosis was asthma for 56.5%, COPD for 12.8% and the remainder (30.7%) were diagnosed simultaneously. Among patients diagnosed in the last 5 years, physicians did not list spirometry as a diagnostic criterion for 35.3%, 13.8% and 26.4% of patients with asthma, asthma+COPD and COPD, respectively (supplementary figure S1).

Patients with asthma+COPD or COPD were more likely to be current or former smokers than those with asthma; however, 6.3% of patients with COPD had never smoked, and 38.1% of patients with asthma were current or former smokers (table 1).

TABLE 1 Demographics and disease history of the NOVELTY population, by physician-assigned diagnosis

	Asthma	Asthma+COPD	COPD	Total
Subjects N[#]	5940	1396	3907	11 243
Female sex	3714 (62.5)	655 (46.9)	1506 (38.5)	5875 (52.3)
Age years	52.0±17.1	64.7±10.3	66.6±9.6	58.7±15.8
Ethnicity				
N with data	5925	1396	3907	11 228
Caucasian	4193 (70.8)	1065 (76.3)	3144 (80.5)	8402 (74.8)
African American	271 (4.6)	57 (4.1)	268 (6.9)	596 (5.3)
North East Asian[¶]	911 (15.4)	200 (14.3)	269 (6.9)	1380 (12.3)
South East Asian	109 (1.8)	24 (1.7)	36 (0.9)	169 (1.5)
Other	441 (7.4)	50 (3.6)	190 (4.9)	681 (6.1)
Smoking status				
N with data	5917	1390	3894	11 201
Never smoked	3652 (61.7)	167 (12.0)	246 (6.3)	4065 (36.3)
Former smoker	1787 (30.2)	882 (63.5)	2495 (64.1)	5164 (46.1)
Current smoker	478 (8.1)	341 (24.5)	1153 (29.6)	1972 (17.6)
Age at diagnosis				
Asthma	33.4±21.4	42.6±23.0	NA	35.2±22.0
COPD	NA	57.2±11.7	58.8±11.9	58.4±11.9
Asthma or COPD	33.4±21.4	42.2±22.4	58.8±11.9	43.4±22.1
Onset of respiratory symptoms at age <12 years	1487 (25.0)	293 (21.0)	176 (4.5)	1956 (17.4)
Family history				
Asthma	2330 (39.2)	541 (38.8)	647 (16.6)	3518 (31.3)
COPD	722 (12.2)	376 (26.9)	937 (24.0)	2035 (18.1)
Allergies	2153 (36.2)	370 (26.5)	475 (12.2)	2998 (26.7)
Physician-assessed severity[+]				
N with data	5935	1392	3905	11 232
Mild	2175 (36.6)	243 (17.5)	1125 (28.8)	3543 (31.5)
Moderate	2108 (35.6)	626 (45.0)	1206 (30.9)	3940 (35.1)
Severe	1652 (27.8)	523 (37.6)	1574 (40.3)	3749 (33.4)

Data are presented as n (%) or mean±SD, unless otherwise stated. For percentages, the denominator is given when different from the total number of patients (N with data, excluding "unknown"). COPD: chronic obstructive pulmonary disease; NA: not applicable. [#]: >90% of patients had complete data for variables; [¶]: including Japanese patients; [+]: recruitment was stratified by diagnosis/severity with the aim of achieving similar numbers of patients in each group; for patients with asthma+COPD, the severity category was the worse of the two physician-assessed severity classifications, and patients with COPD classified as "very severe" were included in the "severe" group. Given the large sample size, any minor differences among categories may be expected to yield a statistically significant result, so for the sake of brevity, p-values for heterogeneity are not provided.

Upper airway comorbidities (allergic rhinitis, recurrent/chronic non-allergic rhinitis/sinusitis and nasal or sinus polyps) were more prevalent among patients with asthma or asthma+COPD than with COPD, whereas cardiovascular comorbidities were more prevalent among patients with asthma+COPD or COPD than with asthma (figure 1).

Blood eosinophil count was similar across physician-assigned diagnoses; eosinophil percentage of total leukocytes was lower among those with COPD, but there was substantial overlap. Blood neutrophil counts were higher among those with asthma+COPD and COPD, and median F_{ENO} was lower among never- or former smokers with COPD than those with asthma (supplementary table S5).

Heterogeneity and overlap by physician-assigned diagnosis and severity

Demographics and disease history

There were no consistent differences in demographics across diagnosis/severity groups (table 2). Approximately one third of patients were obese (body mass index $\geqslant$30.0 kg·m^{-2}); obesity was less common among patients with severe COPD than with severe asthma/asthma+COPD. Current smoking was less common in patients with severe COPD than with mild or moderate COPD. Diagnosis of emphysema increased by increasing severity in asthma+COPD and COPD but was also reported in mild asthma (table 2).

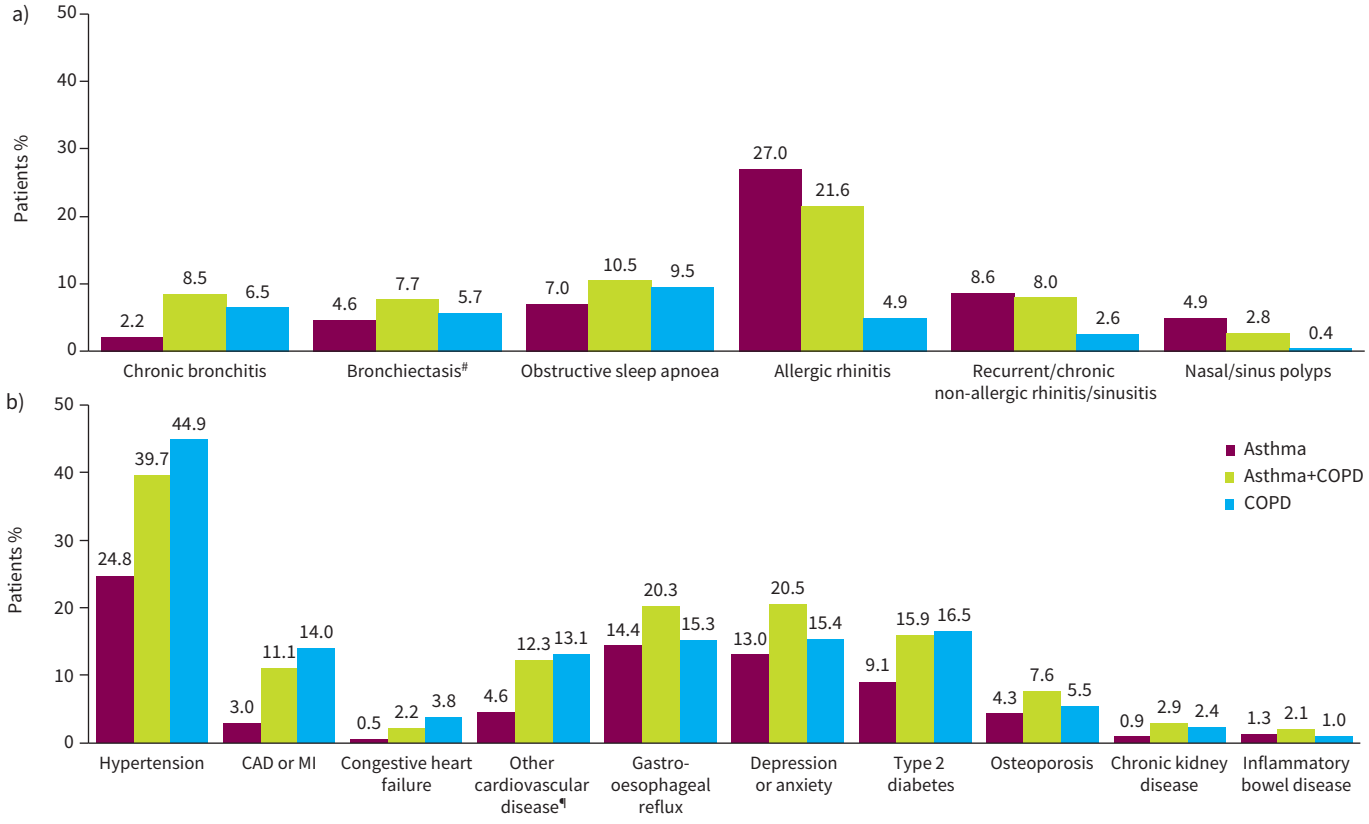

FIGURE 1 a) Respiratory and b) non-respiratory comorbidities in the NOVELTY population, by physician-assigned diagnosis. COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; MI: myocardial infarction. #: from an electronic case report form entry under "Respiratory Comorbidities" and/or from a record of abnormal computed tomography findings; ¶: any cardiovascular disease other than hypertension, CAD, MI or congestive heart failure.

Symptoms, health status and comorbidities

Across the three diagnosis groups, mMRC dyspnoea grade, SGRQ total score and CAAT score were worse with greater physician-assessed severity (figure 2), but there was marked variation within, and overlap between, each diagnosis (supplementary figure S2, supplementary table S5) and diagnosis/severity group (figure 2, supplementary figure S3, supplementary table S6). Within each severity category, patients with asthma+COPD or COPD were more likely to have clinically important dyspnoea (mMRC grade ⩾2), worse HRQoL and worse overall health status than those with asthma (figure 2, supplementary figure S3). Only 38.1% of patients with severe asthma and 24.3% with severe COPD reported their health to be very good/good, and 14.4% and 24.1%, respectively, described their health as poor/very poor (table 2).

Nasal or sinus polyps were reported across all diagnosis/severity groups but were most common in severe asthma (table 2). Cardiovascular comorbidities were more common with greater severity across the total population (supplementary table S6).

Exacerbations

The proportions of patients with ⩾1 or ⩾2 exacerbations in the past 12 months increased across severity groups, but notably included 24.3% and 7.3% of patients with mild asthma and 20.4% and 5.3% of patients with mild COPD, respectively (table 2). Conversely, of patients with severe asthma or severe COPD, 48.3% and 50.6%, respectively, were not reported to have had an exacerbation in the previous 12 months (figure 3). Hospital admissions for exacerbations in the past 12 months also increased across severity groups (table 2).

Spirometric characteristics

Marked heterogeneity was seen in lung function across diagnosis and severity groups, particularly in severe asthma and severe asthma+COPD (figure 4, supplementary figures S2 and S3). Lung function was

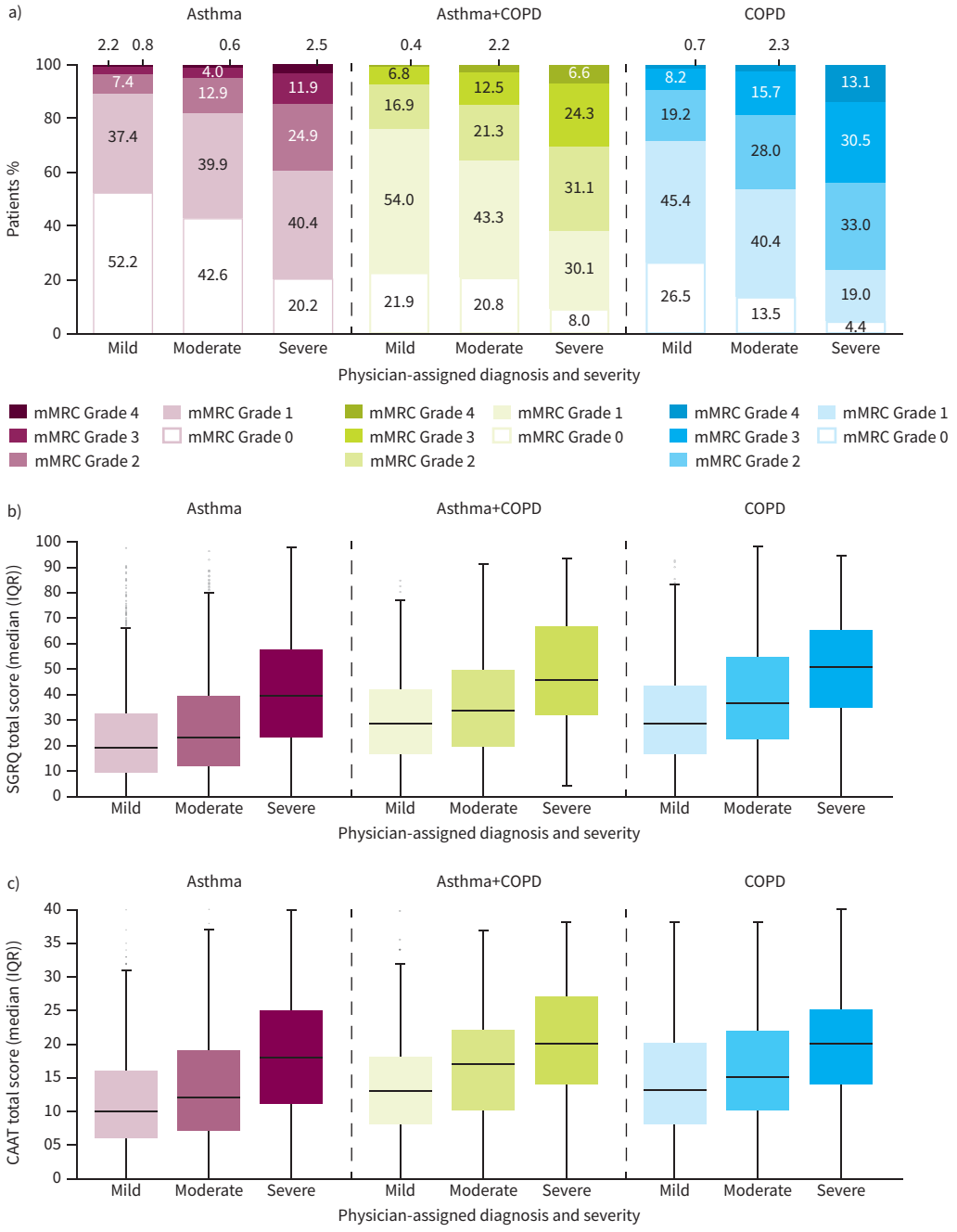

FIGURE 2 Variability in a) modified Medical Research Council (mMRC) dyspnoea grade (available for 96.5% of patients), b) St George's Respiratory Questionnaire (SGRQ) total score (available for 69.3% of patients) and c) Chronic Airways Assessment Test (CAAT[#]) total score (available for 70.0% of patients) by physician-assigned diagnosis and severity.[¶] For b and c, boxes represent the median (interquartile range (Q1–Q3); whiskers extend to 1.5 times the interquartile range, with circles representing individual outliers. COPD: chronic obstructive pulmonary disease. [#]: the CAAT is a trademark of the GlaxoSmithKline group of companies. © 2009 GlaxoSmithKline. All rights reserved. It has been modified from the COPD Assessment Test, with permission, by replacement of the term "COPD" with "chronic airways" and "pulmonary disease" in the questionnaire title and instruction, respectively. [¶]: recruitment was stratified by diagnosis/severity with the aim of achieving similar numbers of patients in each group; for patients with asthma+COPD, the severity category is the worse of the two physician-assessed severity classifications, and patients with COPD classified as "very severe" were included in the "severe" group.

TABLE 2 Clinical characteristics of the NOVELTY population, by physician-assigned diagnosis and severity[#]

	Physician-assigned asthma			Physician-assigned asthma+COPD			Physician-assigned COPD		
	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
Subjects N[¶]	2175	2108	1652	243	626	523	1125	1206	1574
Female sex	1375 (63.2)	1297 (61.5)	1039 (62.9)	120 (49.4)	293 (46.8)	240 (45.9)	448 (39.8)	481 (39.9)	575 (36.5)
Age years	50.0±17.7	53.2±17.0	53.1±16.2	64.0±10.2	65.6±10.1	64.0±10.6	65.1±10.5	66.6±9.6	67.8±8.8
BMI kg·m^{-2}	27.7±6.5	28.1±6.8	28.7±7.0	29.0±6.6	28.6±6.9	28.6±6.4	28.2±6.0	28.3±6.9	26.8±6.3
N with data	2041	1925	1533	235	595	494	1073	1120	1469
<18.5	50 (2.4)	49 (2.5)	49 (3.2)	7 (3.0)	14 (2.4)	11 (2.2)	28 (2.6)	34 (3.0)	105 (7.1)
18.5–<25.0	734 (36.0)	667 (34.6)	431 (28.1)	55 (23.4)	175 (29.4)	139 (28.1)	299 (27.9)	346 (30.9)	531 (36.1)
25.0–<30.0	655 (32.1)	605 (31.4)	511 (33.3)	88 (37.4)	201 (33.8)	166 (33.6)	391 (36.4)	371 (33.1)	451 (30.7)
⩾30.0	602 (29.5)	604 (31.4)	542 (35.4)	85 (36.2)	205 (34.5)	178 (36.0)	355 (33.1)	369 (32.9)	382 (26.0)
Smoking status									
N with data	2170	2101	1644	243	622	521	1118	1204	1572
Never smoked	1364 (62.9)	1245 (59.3)	1042 (63.4)	23 (9.5)	73 (11.7)	71 (13.6)	82 (7.3)	66 (5.5)	98 (6.2)
Former smoker	619 (28.5)	671 (31.9)	496 (30.2)	156 (64.2)	391 (62.9)	333 (63.9)	620 (55.5)	764 (63.5)	1111 (70.7)
Current smoker	187 (8.6)	185 (8.8)	106 (6.4)	64 (26.3)	158 (25.4)	117 (22.5)	416 (37.2)	374 (31.1)	363 (23.1)
Diagnosis of emphysema	44 (2.0)	42 (2.0)	51 (3.1)	50 (20.6)	176 (28.1)	208 (39.8)	269 (23.9)	438 (36.3)	840 (53.4)
⩾1 allergy reported	1383 (63.6)	1340 (63.6)	1076 (65.1)	126 (51.9)	290 (46.3)	299 (57.2)	297 (26.4)	302 (25.0)	315 (20.0)
Allergy testing performed	727 (33.4)	703 (33.3)	753 (45.6)	51 (21.0)	150 (24.0)	153 (29.1)	94 (8.4)	77 (6.4)	109 (6.9)
Atopic[+]	605 (83.2)	558 (79.4)	623 (82.7)	39 (76.5)	97 (64.7)	126 (82.4)	49 (52.1)	46 (59.7)	66 (60.6)
Nasal or sinus polyps	67 (3.1)	87 (4.1)	139 (8.4)	5 (2.1)	23 (3.7)	11 (2.1)	4 (0.4)	4 (0.3)	9 (0.6)
Overall health status[§]									
N with non-missing data	1461	1442	1182	162	434	376	747	820	1121
Very good	226 (15.5)	156 (10.8)	69 (5.8)	13 (8.0)	21 (4.8)	9 (2.4)	67 (9.0)	49 (6.0)	28 (2.5)
Good	665 (45.5)	641 (44.5)	381 (32.2)	69 (42.6)	136 (31.3)	98 (26.1)	276 (36.9)	256 (31.2)	244 (21.8)
Fair	485 (33.2)	522 (36.2)	562 (47.5)	65 (40.1)	217 (50.0)	167 (44.4)	336 (45.0)	382 (46.6)	579 (51.7)
Poor	78 (5.3)	110 (7.6)	142 (12.0)	13 (8.0)	55 (12.7)	79 (21.0)	57 (7.6)	118 (14.4)	224 (20.0)
Very poor	7 (0.5)	13 (0.9)	28 (2.4)	2 (1.2)	5 (1.2)	23 (6.1)	11 (1.5)	15 (1.8)	46 (4.1)
Post-bronchodilator FEV_1 % predicted[f]	93.1±16.4	87.5±18.7	76.1±22.5	84.4±17.2	71.9±18.6	56.2±20.2	80.8±17.8	65.8±17.1	44.4±16.8
Post-bronchodilator FEV_1/FVC[f]	0.78±0.09	0.75±0.11	0.69±0.14	0.67±0.12	0.62±0.13	0.53±0.16	0.68±0.11	0.60±0.13	0.46±0.14
N with data (for <0.7)	1797	1727	1413	204	534	446	956	993	1336
<0.7	288 (16.0)	471 (27.3)	637 (45.1)	113 (55.4)	386 (72.3)	371 (83.2)	514 (53.8)	716 (72.1)	1233 (92.3)
N with data (for LLN)	1755	1685	1380	201	516	430	941	962	1297
<LLN	203 (11.6)	366 (21.7)	549 (39.8)	83 (41.3)	302 (58.5)	324 (75.3)	340 (36.1)	576 (59.9)	1130 (87.1)
Bronchodilator responsiveness %	5.4±8.4	5.9±9.0	8.3±11.0	6.3±8.6	7.3±9.7	10.1±13.5	4.8±10.0	5.7±11.1	8.4±12.5
N with data	1724	1672	1379	196	513	426	921	931	1267
>12% and >200 mL	214 (12.4)	237 (14.2)	308 (22.3)	29 (14.8)	91 (17.7)	97 (22.8)	109 (11.8)	129 (13.9)	171 (13.5)
Exacerbations in the past 12 months[##]	0.4±1.1	0.5±1.2	1.2±2.0	0.5±0.9	0.9±1.7	1.4±2.1	0.3±0.7	0.5±0.9	1.0±1.6
N with data	2166	2089	1635	242	624	522	1112	1193	1565
⩾1	527 (24.3)	642 (30.7)	798 (50.9)	84 (34.7)	258 (41.3)	310 (59.4)	227 (20.4)	354 (29.7)	796 (50.9)
⩾2	158 (7.3)	240 (11.5)	434 (26.5)	32 (13.2)	121 (19.4)	158 (30.3)	59 (5.3)	113 (9.5)	342 (21.9)
Healthcare utilisation									
N with data	2166	2089	1635	242	624	522	1112	1193	1565
⩾1 hospital admission related to an exacerbation in the past 12 months	27 (1.2)	47 (2.2)	147 (8.9)	8 (3.3)	47 (7.5)	70 (13.4)	33 (3.0)	85 (7.1)	284 (18.1)

Data are presented as n (%) or mean±SD, unless otherwise stated. For percentages, the denominator is given when different from the total number of patients (N with data, excluding "unknown"). COPD: chronic obstructive pulmonary disease; BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; LLN: lower limit of normal. [#]: recruitment was stratified by diagnosis/severity with the aim of achieving similar numbers of patients in each group; for patients with asthma+COPD, the severity category is the worse of the two physician-assigned severity classifications, and patients with COPD classified as "very severe" were included in the "severe" group; [¶]: ~80% of patients had post-bronchodilator spirometry data, 70% had patient-reported outcome data and >90% had complete data for other variables; [+]: data presented as n (% of those with allergy testing); [§]: data presented as n (% of patients with non-missing data), from the question that precedes the St George's Respiratory Questionnaire: "*please tick in one box to show how you describe your current health*"; [f]: Global Lung Function Initiative multi-ethnic reference equations were used to calculate % predicted values [13]; [##]: includes mild, moderate and severe exacerbations from the following question in the electronic case report form: "*During the past 12 months, on how many occasions has your patient experienced an exacerbation of their asthma or COPD beyond the patient's usual day-to-day variance?*"

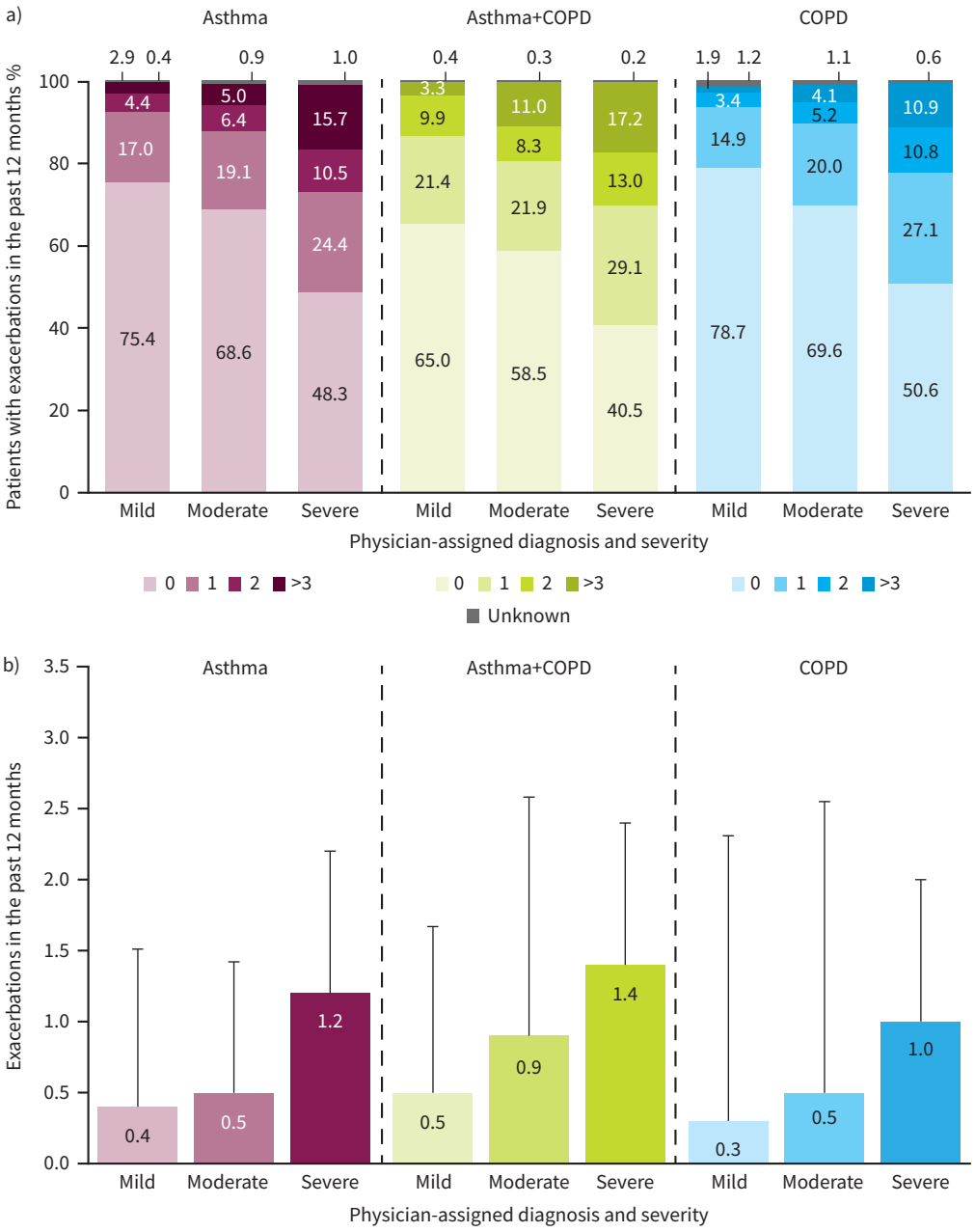

FIGURE 3 Frequency distribution by a) the number of exacerbations[#] and b) the mean number of exacerbations (among all patients, including those with no exacerbations) in the past 12 months, by physician-assigned diagnosis and severity.[¶] In b, data are presented as mean+SD. COPD: chronic obstructive pulmonary disease. [#]: exacerbations include mild, moderate and severe exacerbations, from the following question in the electronic case report form: "*During the past 12 months, on how many occasions has your patient experienced an exacerbation of their asthma or COPD beyond the patient's usual day-to-day variance?*"; [¶]: recruitment was stratified by diagnosis/severity with the aim of achieving similar numbers of patients in each group; for patients with asthma+COPD, severity was based on the more severe of the physician's assessed severity for asthma and for COPD, and patients with COPD classified as "very severe" were included in the "severe" group.

lower with greater physician-assessed severity, but reduced post-bronchodilator FEV_1/FVC and FEV_1 were prevalent across all severity groups, particularly in asthma+COPD and COPD (table 2, figure 4, supplementary tables S4 and S5 and supplementary figures S2 and S3).

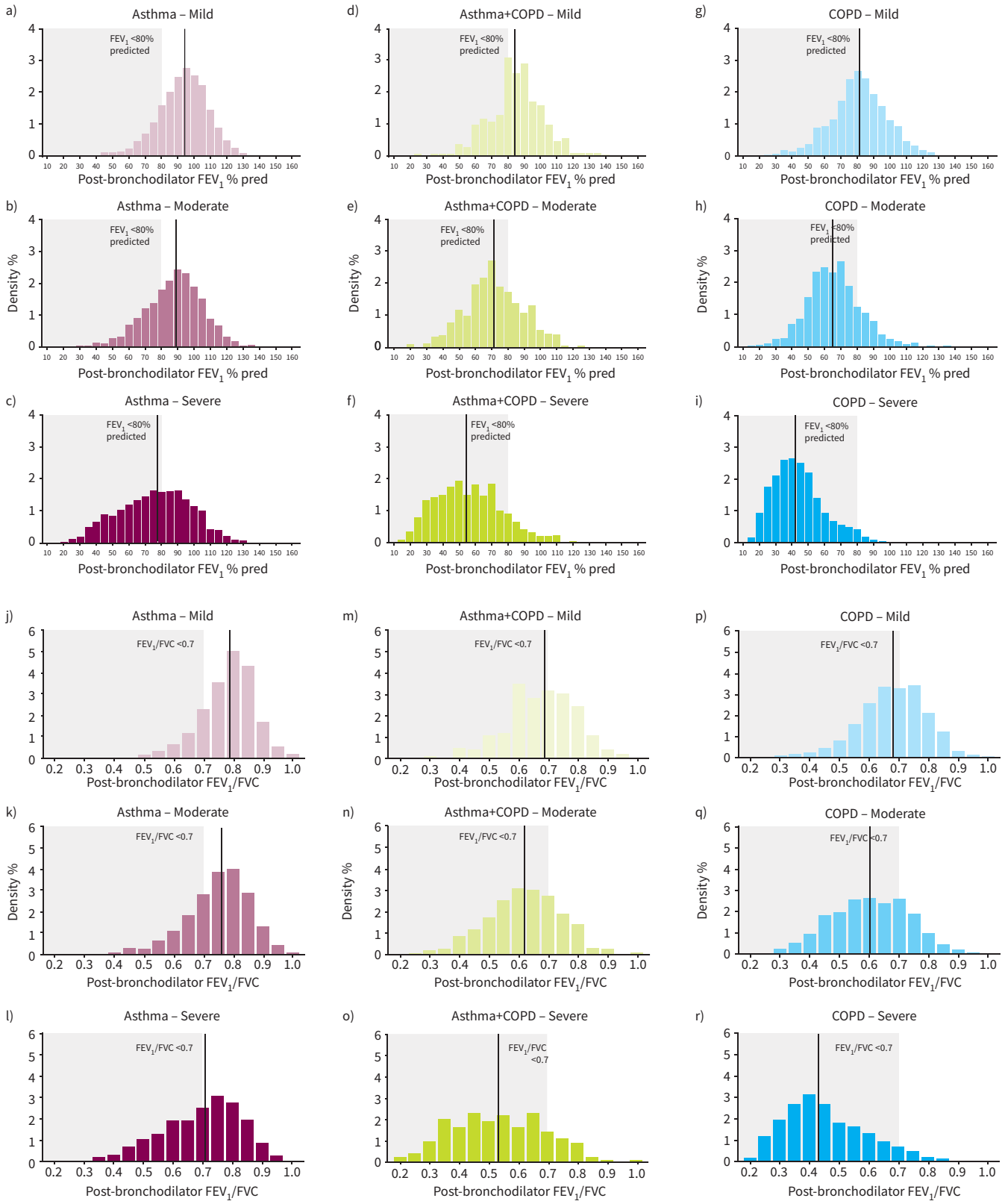

FIGURE 4 Heterogeneity in a–i) post-bronchodilator forced expiratory volume in 1 s (FEV_1), j–r) post-bronchodilator FEV_1/forced vital capacity (FVC) and s–aa) bronchodilator responsiveness, by physician-assigned diagnosis and severity. For continuous data, density is calculated as frequency divided by category width. The solid black lines show the median values. Grey shading shows the spirometric thresholds used in asthma/chronic obstructive pulmonary disease (COPD) diagnostic criteria [2, 3]. See supplementary table S3 for the number of patients with post-bronchodilator spirometry data. Global Lung Function Initiative multi-ethnic reference equations were used to calculate % predicted values [13].

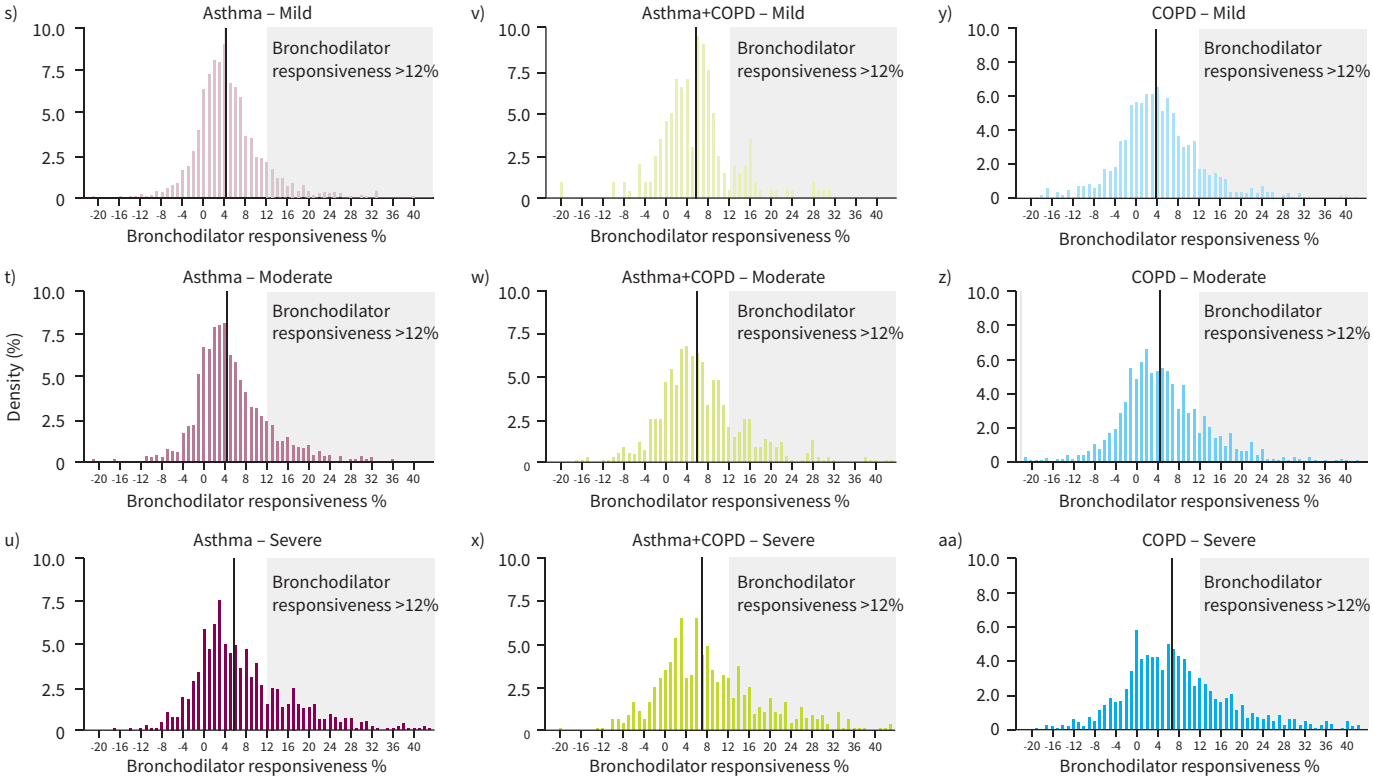

FIGURE 4 Continued.

Among patients with a diagnosis of COPD, only 63.9% had persistent airflow limitation, defined as post-bronchodilator FEV_1/FVC <LLN (or 75.0% with FEV_1/FVC <0.7), with similar findings for asthma+COPD (supplementary table S5). Among patients with asthma, 23.2% (<LLN) and 28.3% (<0.7) had persistent airflow limitation (supplementary table S5).

The distribution of bronchodilator responsiveness (available for 80.3% of patients (n=9034)) overlapped across physician-assigned diagnosis and severity groups (supplementary figures S2 and S3), and 13.1% of patients with COPD had bronchodilator responsiveness of >12% and >200 mL at the baseline visit, compared with 19.1% with asthma+COPD and 15.9% of patients with asthma (supplementary table S5). Among patients with asthma or asthma+COPD, bronchodilator responsiveness increased with increasing physician-assessed severity (table 2, supplementary figure S3).

Medications

Overall, intensity of therapy increased with increasing physician-assessed severity across diagnosis groups, although marked heterogeneity was observed within diagnosis and severity groups (table 3). Patients classified as having mild asthma were most commonly receiving medium/high-dose inhaled corticosteroid (ICS) long-acting β_2-agonists (LABA) (25.6%), low-dose ICS-LABA (22.5%) or short-acting bronchodilators without ICS (16.0%), but 2.1% were receiving maintenance oral corticosteroids (OCS). Among those with severe asthma, 39.3% were receiving leukotriene modifiers, 30.3% biologic therapy and 13.4% maintenance OCS. Patients with mild COPD were commonly taking short-acting bronchodilators (29.9%) or LABAs and/or long-acting muscarinic antagonists (LAMA) (41.8%) without ICS, but this was also the treatment for 17.0% and 25.1%, respectively, of patients with severe COPD. The most common treatment among patients with severe COPD was triple therapy (ICS+LABA+LAMA) (49.5%). Triple therapy was also being taken by 16.6% of patients with severe asthma and 50.1% with severe asthma+COPD, but also by 23.7% with mild asthma+COPD. Overall, 10.9%, 15.9% and 44.0% of patients with asthma, asthma+COPD and COPD, respectively, were not taking any ICS-containing therapy (supplementary table S6).

Biomarkers

There was little variation in blood eosinophil counts by severity, even after excluding patients taking maintenance OCS or anti-interleukin 5 therapy, but blood neutrophil counts increased with

TABLE 3 Medications and biomarkers in the NOVELTY population, by physician-assigned diagnosis and severity[#]

	Physician-assigned asthma			Physician-assigned asthma+COPD			Physician-assigned COPD		
	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
Subjects N[¶]	2175	2108	1652	243	626	523	1125	1206	1574
Respiratory medications[+]									
N with medication data	2059	2082	1622	236	614	519	935	1149	1547
N with ICS dose data	1820	1882	1499	219	563	477	880	1082	1450
No ICS[§]	390 (18.9)	134 (6.4)	103 (6.4)	65 (27.5)	98 (16.0)	55 (10.6)	543 (58.1)	587 (51.1)	469 (30.3)
Short-acting BD, no ICS[§]	329 (16.0)	109 (5.2)	50 (3.1)	45 (19.1)	72 (11.7)	31 (6.0)	280 (29.9)	296 (25.8)	263 (17.0)
LABA and/or LAMA, no ICS[§]	18 (0.9)	13 (0.6)	18 (1.1)	32 (13.6)	66 (10.7)	39 (7.5)	391 (41.8)	497 (43.3)	388 (25.1)
Low-dose ICS	229 (12.6)	60 (3.2)	12 (0.8)	6 (2.7)	7 (1.2)	0 (0.0)	20 (2.3)	5 (0.5)	6 (0.4)
Low-dose ICS+LABA	410 (22.5)	444 (23.6)	106 (7.1)	32 (14.6)	58 (10.3)	20 (4.2)	75 (8.5)	61 (5.6)	38 (2.6)
Med/high-dose ICS+LABA	466 (25.6)	855 (45.4)	443 (29.6)	44 (20.1)	107 (19.0)	66 (13.8)	76 (8.6)	77 (7.1)	112 (7.7)
ICS+LABA+LAMA[f]	61 (3.0)	158 (7.6)	270 (16.6)	56 (23.7)	266 (43.3)	260 (50.1)	140 (15.0)	346 (30.1)	766 (49.5)
Maintenance OCS	43 (2.1)	80 (3.8)	217 (13.4)	3 (1.3)	22 (3.6)	58 (11.2)	10 (1.1)	17 (1.5)	70 (4.5)
Biologic therapy	14 (0.7)	61 (2.9)	491 (30.3)	2 (0.8)	7 (1.1)	49 (9.4)	0 (0.0)	1 (0.1)	2 (0.1)
Leukotriene modifier	415 (20.2)	617 (29.6)	638 (39.3)	23 (9.7)	112 (18.2)	157 (30.3)	26 (2.8)	33 (2.9)	53 (3.4)
Blood eosinophil count $10^9 \cdot \mu L^{-1}$	0.16±2.00	0.17±2.10	0.18±2.19	0.15±1.89	0.16±1.97	0.16±2.12	0.14±1.88	0.15±1.90	0.15±1.89
N without OCS, anti-IL-4/4R or anti-IL5/5R	917	839	600	126	325	257	471	515	730
Excluding patients with OCS, anti-IL-4/4R or anti-IL5/5R	0.16±1.99	0.17±2.09	0.19±2.07	0.16±1.87	0.16±1.95	0.17±2.14	0.14±1.9	0.15±1.91	0.15±1.89
Blood eosinophil proportion (% of total leukocytes)	2.34±1.95	2.45±2.04	2.09±2.22	2.17±1.86	2.15±1.99	2.02±2.16	1.8±1.85	1.86±1.87	1.67±1.86
Excluding patients with OCS, anti-IL-4/4R or anti-IL5/5R	2.34±1.94	2.45±2.02	2.35±2.06	2.30±1.86	2.18±1.97	2.05±2.15	1.85±1.86	1.88±1.86	1.69±1.86
Blood neutrophil count $10^9 \cdot \mu L^{-1}$	3.84±1.41	4.00±1.43	4.5±1.50	4.27±1.45	4.52±1.46	4.7±1.45	4.26±1.39	4.42±1.42	4.89±1.44
Blood neutrophil proportion (% of total leukocytes)	55.16±1.19	56.06±1.17	51.14±1.17	61.39±1.17	58.46±1.16	56.76±1.18	51.28±1.15	53.43±1.19	52.56±1.17
F_{ENO} ppb, median (IQR)									
Excluding current smokers	22 (14–38)	23 (14–39)	25 (15–44)	20 (13–31)	21 (13–37)	18 (12–29)	19 (12–28)	18 (12–28)	16 (10–25)
Current smokers	16 (8.75–30)	12 (7–23)	15 (7–28)	13 (7–19.25)	10 (6–17.5)	9 (6–16)	11 (7–17)	10 (6–16)	10 (6–17)

Data are presented as n (%) or geometric mean±geometric SD, unless otherwise indicated. For percentages, the denominator is given when different from the total number of patients (N with data, excluding "unknown"). COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; BD: bronchodilator; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; OCS: oral corticosteroid; IL-4/4R: interleukin-4 or interleukin-4 receptor; IL-5/5R: interleukin-5 or interleukin-5 receptor; IQR: interquartile range; F_{ENO}: fractional exhaled nitric oxide. [#]: recruitment was stratified by diagnosis/severity with the aim of achieving similar numbers of patients in each group; for patients with asthma+COPD, the severity category is the worse of the two physician-assigned severity classifications, and patients with COPD classified as "very severe" were included in the "severe" group; [¶]: ~50% of patients had biomarker data; [+]: medication categories are defined in supplementary table S2 and ICS dose was classified according to Global Initiative for Asthma 2019 definition [37]; [§]: "no ICS" was defined as neither maintenance nor reliever ICS; [f]: without maintenance OCS or biologic therapy.

physician-assessed severity across all diagnoses; there were no clear patterns for eosinophil and neutrophil percentages by severity (table 3). Levels of F_{ENO} among non-smokers were similar across diagnosis/severity groups, except for lower levels in patients with severe COPD (table 3), consistent with their lower lung function (table 2).

Factors associated with physician-assessed severity

In multivariable ordinal regression analysis among all patients with asthma or COPD, several clinical and spirometric factors were associated with greater physician-assessed severity (supplementary figure S4a). Notably, current smoking was associated with a lower severity classification than never/former smoking;

obesity was also independently associated with lower severity. Supplementary figure S4 also shows significant factors for asthma and COPD separately. Results of the univariate analysis are shown in supplementary figure S5.

Discussion

The results of this cross-sectional analysis of patients with diagnoses of asthma and/or COPD, recruited from primary care, specialist care and other settings, demonstrate marked heterogeneity within, and overlap between, each diagnostic label and physician-assessed severity category. The features typically used to define asthma and COPD in clinical trials and mechanistic studies were found across all subgroups of patients. This indicates that the historical labels of "asthma" and "COPD" and the severity classifications used in clinical practice do not identify clinically distinct populations. Furthermore, the findings confirm that there is a clinical and healthcare utilisation burden of symptoms and exacerbations, even among patients considered by their physician to have mild disease. These findings have important implications for asthma and COPD management, because they demonstrate that patients with specific risks and treatment needs are not clearly distinguishable from other groups in clinical practice using conventional criteria. NOVELTY thus fills a conspicuous gap in evidence about asthma and/or COPD in broad populations, a gap that, to date, has limited progress in understanding the underlying mechanisms and progression of new therapies. Our findings emphasise the need for a deeper understanding of phenotypes and endotypes of asthma and/or COPD, and challenge the specificity and utility of conventional classifications of "asthma" and "COPD".

Most previous studies describing characteristics of patients with asthma or COPD (including large cohort studies such as SPIROMICS and U-BIOPRED) have focused on selected populations with either diagnosis, based on conventional criteria, from a particular care setting or geographic region, or focused on severe disease [9–11]. By contrast, NOVELTY enrolled patients with physician diagnoses of asthma and/or COPD, with very few inclusion and exclusion criteria, from a variety of clinical and healthcare settings globally, allowing future investigation of regional differences in the features and management of asthma and/or COPD. Almost half were recruited from primary care, where most patients with asthma or COPD are treated. This supports the generalisability of present and future NOVELTY findings to real-world clinical practice.

To fulfil the aims of NOVELTY, patients were recruited based on physician-assigned diagnosis, with no diagnostic criteria specified. At baseline, fewer than two thirds of patients with COPD had persistent airflow limitation (post-bronchodilator FEV_1/FVC <LLN), which is consistent with other recent findings [18, 19]. While variability in post-bronchodilator FEV_1/FVC over time [20, 21] may have contributed, spirometry is often not used in clinical practice; however, the concept of defining COPD, a complex and often systemic disease, by a single number should be challenged [20]. Furthermore, almost one quarter of patients labelled as having asthma and 62% of those labelled as having asthma+COPD demonstrated persistent airflow limitation, and significant bronchodilator responsiveness was found in 15.9% of patients labelled as having asthma and 13.1% of patients labelled as having COPD, slightly lower than in other large, global population studies [22]. Asthma guidelines emphasise the importance of confirming the diagnosis before treatment is started or the effects of remodelling and ageing are superimposed, and that a single test may not be sufficient [2], yet bronchodilator responsiveness continues to be required for eligibility for clinical asthma studies.

In this baseline analysis, clinical, physiological and biomarker characteristics overlapped extensively between patients with physician-assigned diagnoses of asthma, asthma+COPD and COPD. Features such as allergic rhinitis and nasal polyposis, commonly associated with asthma [23], and smoking and emphysema, commonly associated with COPD [24], were present across all diagnoses. Blood eosinophil counts were similar across diagnosis and severity groups, but blood neutrophil counts were higher with higher physician-assessed severity, which is consistent with recent observations that higher blood neutrophil counts in COPD are associated with lower lung function [25], and in asthma with risk of exacerbations requiring OCS [26]. These findings support the emerging view that conventional diagnostic categories in asthma and COPD are oversimplified and generalise complex and heterogeneous conditions [7]. The use of these diagnostic labels in study design reduces opportunities to explore important underlying mechanistic pathways and more targeted treatment options across the spectrum of obstructive lung disease. NOVELTY aims to address this problem with its broad, unrestricted patient population, long-term data collection and analysis of known and emerging biomarkers [12]. Future analyses of NOVELTY data will aim to find new ways of classifying patients according to phenotypes and endotypes rather than by diagnostic label alone, to support the development of precision medicine and point-of-care biomarkers for obstructive lung disease [8, 27, 28].

In the meantime, though, the labels of asthma and asthma+COPD remain clinically important because, while the specific mechanisms are yet to be identified, patients with these diagnoses have a significantly increased risk of death or hospitalisation if treated with LABA alone (without ICS) [29–31], compared with patients with a diagnosis only of COPD [29, 31]. In the present analysis, 10.9% of patients with asthma and 15.9% with asthma+COPD were not receiving any ICS. There was also evidence suggestive of both over- and under-treatment, relative to severity, across all diagnostic groups.

To date, few data are available to guide treatment in patients with features of both asthma and COPD [32] (often given interim descriptive labels of asthma–COPD overlap or asthma+COPD [2]). Most such NOVELTY patients had received the asthma diagnosis first, suggesting that the COPD diagnosis was added when symptoms and/or airflow limitation became persistent. Among patients with asthma+COPD, physiological and clinical features lay between those of patients with asthma only and COPD only, but symptoms, HRQoL and non-respiratory comorbidities were more similar to COPD. However, as in previous reports [33], there was a greater burden of exacerbations with asthma+COPD than with either diagnosis alone.

Comparison of baseline characteristics by physician-assessed severity showed clear gradations by severity in symptoms, HRQoL, lung function and exacerbations. Severity category was also associated with diagnosis-aligned features that are known to be associated with more troublesome disease, such as allergic/non-allergic upper airway disease (for asthma) and emphysema (for COPD). However, some patients with physician-assessed mild asthma had features associated with poor outcomes (*e.g.* low lung function and exacerbations). This suggests that the criteria used by physicians to assess severity and thus make treatment decisions do not adequately identify patients at risk of adverse outcomes, including death [7]. Bloom and colleagues [34, 35] have reported that some patients with mild asthma (defined by treatment level) experience severe exacerbations, and a recent meta-analysis [36] identified a wide range of exacerbation rates in mild asthma.

The strengths of NOVELTY are that it is a large, global, longitudinal observational study of patients recruited from clinical practice, almost half from primary care, without the limitations of current severity classifications or the criteria that are recommended in clinical guidelines for initial diagnosis at the time of first presentation, which are often required by regulators for pharmacotherapy studies regardless of disease duration. Inclusion of current smokers with asthma and never-smokers with COPD enables a broader investigation of mechanisms and perspective on comorbidity patterns. The use of "diagnosis-agnostic" tools for symptoms and health status (mMRC, SGRQ and CAAT) ensures that findings can be reported across the entire population, regardless of diagnostic label. These features increase the generalisability of the present and future findings to real-world clinical practice across the spectrum of asthma and/or COPD.

Limitations include that the NOVELTY population is not a random sample (recruitment was stratified in each country/region with target numbers by diagnosis/severity to ensure sufficient subgroup samples), so whole-population results cannot be used to infer prevalence. Some baseline variables, such as exacerbations in the past 12 months, were subject to recall bias; future analysis of the prospective longitudinal follow-up data will provide more accurate data. Finally, because NOVELTY is an observational study of patients in a real-world setting, these findings represent the characteristics of patients already on treatment, which may differ from those present at the time of diagnosis.

Conclusions

This analysis of baseline characteristics in the NOVELTY population demonstrates marked heterogeneity *within* and considerable overlap *between* physician-assigned diagnoses of asthma and/or COPD, including by physician-assessed severity. These findings indicate that the diagnostic and severity classifications used by physicians in real-world clinical practice poorly differentiate between clinical phenotypes, potentially leading to unsuitable or unsafe treatment decisions. This emphasises the importance of identifying and validating biomarkers to identify target populations (particularly those characterised by different trajectories over time) from which molecular endotypes of asthma and/or COPD can be elucidated, and more precise clinical classification and treatment decisions can be made.

Acknowledgements: The authors would like to thank the patients who participated in this study and the NOVELTY study investigators (listed below). The authors also thank Richard J. Martin (National Jewish Health and the University of Colorado, Denver, CO, USA) for his contribution to the NOVELTY study design and interpretation of data as a member of the NOVELTY Scientific Committee, and Laura Belton and Crina Samarghitean (AstraZeneca) for their critical review of the manuscript. Medical writing support, under the direction of the authors, was provided by Nina Divorty, PhD, CMC Connect, McCann Health Medical Communications, and was funded by

AstraZeneca, Cambridge, UK, in accordance with Good Publication Practice (GPP3) guidelines (*Ann Intern Med* 2015; 163: 461–464). J. Vestbo is supported by the NIHR Manchester Biomedical Research Centre and the NIHR Manchester Clinical Research Facility.

List of NOVELTY study investigators: Gabriel Benhabib, Xavier Bocca Ruiz, Ricardo del Olmo, Raul Eduardo Lisanti, Gustavo Marino, Walter Mattarucco, Juan Nogueira, Maria Parody, Pablo Pascale, Pablo Rodriguez, Damian Silva, Graciela Svetliza, Carlos F. Victorio, Roxana Willigs Rolon, Anahi Yañez (Argentina); Stuart Baines, Simon Bowler, Peter Bremner, Sheetal Bull, Patrick Carroll, Mariam Chaalan, Claude Farah, Gary Hammerschlag, Kerry Hancock, Zinta Harrington, Gregory Katsoulotos, Joshua Kim, David Langton, Donald Lee, Matthew Peters, Lakshman Prassad, Helen Reddel, Dimitar Sajkov, Francis Santiago, Frederick Graham Simpson, Sze Tai, Paul Thomas, Peter Wark (Australia); José Eduardo Delfini Cançado, Thúlio Cunha, Marina Lima, Alexandre Pinto Cardoso, Marcelo Rabahi (Brazil); Syed Anees, John Bertley, Alan Bell, Amarjit Cheema, Guy Chouinard, Michael Csanadi, Anil Dhar, Ripple Dhillon, J. Mark FitzGerald, David Kanawaty, Allan Kelly, William Killorn, Daniel Landry, Robert Luton, Piushkumar Mandhane, Andrew McIvor, Bonavuth Pek, Robert Petrella, Daniel Stollery (Canada); Meihua Chen, Yan Chen, Wei Gu, Kim Ming Christopher Hui, Manxiang Li, Shiyue Li, Ma Lijun, Guangyue Qin, Weidong Song, Wei Tan, Yijun Tang, Chen Wang, Tan Wang, Fuqiang Wen, Feng Wu, PingChao Xiang, Zuke Xiao, Shengdao Xiong, Jinghua Yang, Jingping Yang, Caiqing Zhang, Min Zhang, Ping Zhang, Wei Zhang, Xiaohe Zheng, Dan Zhu (China; data for patients from China were excluded from the present analyses due to a change in regulations about data transfer in May 2019); Fabio Bolivar Grimaldos, Alejandra Cañas Arboleda, Carlos Matiz Bueno, Dora Molina de Salazar (Colombia); Elisabeth Bendstrup, Ole Hilberg, Carsten Kjellerup, Ulla Weinreich (Denmark); Philippe Bonniaud, Olivier Brun, Pierre-Régis Burgel, Christos Chouaid, Francis Couturaud, Jacques de Blic, Didier Debieuvre, Dominique Delsart, Axelle Demaegdt, Pascal Demoly, Antoine Deschildre, Gilles Devouassoux, Carole Egron, Lionel Falchero, François Goupil, Romain Kessler, Pascal Le Roux, Pascal Mabire, Guillaume Mahay, Stéphanie Martinez, Boris Melloni, Laurent Moreau, Chantal Raherison, Emilie Riviere, Pauline Roux-Claudé, Michel Soulier, Guillaume Vignal, Azzedine Yaici (France); Sven Philip Aries, Robert Bals, Ekkehard Beck, Andreas Deimling, Jan Feimer, Vera Grimm-Sachs, Gesine Groth, Felix Herth, Gerhard Hoheisel, Frank Kanniess, Thomas Lienert, Silke Mronga, Jörg Reinhardt, Christian Schlenska, Christoph Stolpe, Ishak Teber, Hartmut Timmermann, Thomas Ulrich, Peter Velling, Sabina Wehgartner-Winkler, Juergen Welling, Ernst-Joachim Winkelmann (Germany); Carlo Barbetta, Fulvio Braido, Vittorio Cardaci, Enrico Maria Clini, Maria Teresa Costantino, Giuseppina Cuttitta, Mario di Gioacchino, Alessandro Fois, Maria Pia Foschino-Barbaro, Enrico Gammeri, Riccardo Inchingolo, Federico Lavorini, Antonio Molino, Eleonora Nucera, Alberto Papi, Vincenzo Patella, Alberto Pesci, Fabio Ricciardolo, Paola Rogliani, Riccardo Sarzani, Carlo Vancheri, Rigoletta Vincenti (Italy); Takeo Endo, Masaki Fujita, Yu Hara, Takahiko Horiguchi, Keita Hosoi, Yumiko Ide, Minehiko Inomata, Hiromasa Inoue, Koji Inoue, Sumito Inoue, Motokazu Kato, Masayuki Kawasaki, Tomotaka Kawayama, Toshiyuki Kita, Kanako Kobayashi, Hiroshi Koto, Koichi Nishi, Junpei Saito, Yasuo Shimizu, Toshihiro Shirai, Naruhiko Sugihara, Ken-ichi Takahashi, Hiroyuki Tashimo, Keisuke Tomii, Takashi Yamada, Masaru Yanai (Japan); Ruth Cerino Javier, Alfredo Domínguez Peregrina, Marco Fernández Corzo, Efraín Montano Gonzalez, Alejandra Ramírez-Venegas, Adrian Rendon (Mexico); Willem Boersma, R.S. Djamin, Michiel Eijsvogel, Frits Franssen, Martijn Goosens, Lidwien Graat-Verboom, Johannes in 't Veen, Rob Janssen, Kim Kuppens, Maarten van den Berge, Mario van de Ven (The Netherlands); Ole Petter Brunstad, Gunnar Einvik, Kristian Jong Høines, Alamdar Khusrawi, Torbjorn Oien (Norway); Yoon-Seok Chang, Young Joo Cho, Yong Il Hwang, Woo Jin Kim, Young-Il Koh, Byung-Jae Lee, Kwan-Ho Lee, Sang-Pyo Lee, Yong Chul Lee, Seong Yong Lim, Kyung Hun Min, Yeon-Mok Oh, Choon-Sik Park, Hae-Sim Park, Heung-Woo Park, Chin Kook Rhee, Ho Joo Yoon, Hyoung-Kyu Yoon (South Korea); Alvar Agusti García-Navarro, Rubén Andújar, Laura Anoro, María Buendía García, Paloma Campo Mozo, Sergio Campos, Francisco Casas Maldonado, Manuel Castilla Martínez, Carolina Cisneros Serrano, Lorena Comeche Casanova, Dolores Corbacho, Felix Del Campo Matías, Jose Echave-Sustaeta, Gloria Francisco Corral, Pedro Gamboa Setién, Marta García Clemente, Ignacio García Núñez, Jose García Robaina, Mercedes García Salmones, Jose Maria Marín Trigo, Marta Nuñez Fernandez, Sara Nuñez Palomo, José Olaguibel Rivera, Luis Pérez de Llano, Ana Pueyo Bastida, Ana Rañó, José Rodríguez González-Moro, Albert Roger Reig, José Velasco Garrido (Spain); Dan Curiac, Christer Janson, Cornelia Lif-Tiberg, Anders Luts, Lennart Råhlen, Stefan Rustscheff (Sweden); Frances Adams, Drew Bradman, Emma Broughton, John Cosgrove, Patrick Flood-Page, Liz Fuller, Timothy Harrison, David Hartley, Keith Hattotuwa, Gareth Jones, Keir Lewis, Lorcan McGarvey, Alyn Morice, Preeti Pandya, Manish Patel, Kay Roy, Ramamurthy Sathyamurthy, Swaminathan Thiagarajan, Alice Turner, Jørgen Vestbo, Wisia Wedzicha, Tom Wilkinson, Pete Wilson (UK); Lo'Ay Al-Asadi, James Anholm, Frank Averill, Sandeep Bansal, Alan Baptist, Colin Campbell, Michael A. Campos, Bradley Chipps, Gretchen Crook, Samuel DeLeon, Alain Eid, Ellen Epstein, Stephen Fritz, Hoadley Harris, Mitzie Hewitt, Fernando Holguin, Golda Hudes, Richard Jackson, Alan Kaufman, David Kaufman, Ari Klapholz, Harshavardhan Krishna, Daria Lee, Robert Lin, Diego Maselli-Caceres, Vinay Mehta, James N. Moy, Ugo Nwokoro, Purvi Parikh. Sudhir Parikh, Frank Perrino, James Ruhlmann, Catherine Sassoon, Russell A. Settipane, Daniel Sousa, Peruvemba Sriram, Richard Wachs (USA).

ClinicalTrials.gov identifier: NCT02760329. Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data-sharing policy described at https://astrazenecagrouptrials.

pharmacm.com/ST/Submission/Disclosure. The study protocol is available at https://astrazenecagrouptrials.pharmacm.com.

Author contributions: All authors, including those who were AstraZeneca employees, contributed to the study design, analysis and/or interpretation of data and critical review of the manuscript. All authors had full access to, and contributed to the interpretation of, all data reported herein. The corresponding author had final responsibility for the decision to submit for publication.

Conflict of interest: H.K. Reddel reports grants, personal fees and non-financial support from AstraZeneca, during the conduct of the study; grants and personal fees for data monitoring committee work, advisory board work and providing independent medical education from AstraZeneca and GlaxoSmithKline, personal fees for data monitoring committee work from Merck, personal fees for data monitoring committee work, advisory board work and grant for registry from Novartis, personal fees for providing independent medical education from Teva, personal fees for advisory board work and providing independent medical education from Boehringer Ingelheim, and personal fees for advisory board work from Sanofi Genzyme and Chiesi, outside the submitted work; and is Chair of the GINA Scientific Committee and a member of the GINA Board. J. Vestbo reports personal fees for steering committee work from AstraZeneca, during the conduct of the study; and personal fees for consultancy and lectures from GlaxoSmithKline, Chiesi Pharmaceuticals, Novartis and AstraZeneca, and grants and personal fees for consultancy and lectures from Boehringer Ingelheim, outside the submitted work. A. Agusti reports personal fees for scientific committee work from AstraZeneca, during the conduct of the study; and grants and personal fees for lectures and advisory board work from GlaxoSmithKline and Menarini, and personal fees for lectures and advisory board work from Chiesi, outside the submitted work. G.P. Anderson reports personal fees for consultancy and share options from Pieris Pharmaceuticals, ENA Therapeutics and ENA Respiratory, personal fees for scientific committee work from AstraZeneca, and personal fees for lectures from GlaxoSmithKline, AstraZeneca, Menarini and Novartis, outside the submitted work; and has US Patent 7,455,836 licensed to MorphoSys, sublicensed to GlaxoSmithKline. A.T. Bansal has nothing to disclose. R. Beasley reports personal fees for steering committee work from AstraZeneca, during the conduct of the study; and grants and personal fees from AstraZeneca and GlaxoSmithKline, personal fees from Avillion and Theravance, and grants from Genentech, outside the submitted work. E.H. Bel reports grants and personal fees from AstraZeneca, GlaxoSmithKline, Novartis and Teva, and personal fees from Sanofi/Regeneron, Sterna and Chiesi, outside the submitted work. C. Janson reports personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis and Teva, outside the submitted work. B. Make reports grants, non-financial support and other (advisory board and presentations) from AstraZeneca, grants, non-financial support and other from GlaxoSmithKline, non-financial support for data monitoring committee work from Spiration, grants, non-financial support and other (advisory board) from Sunovion, other (CME activity) from Mt. Sinai, Web MD, National Jewish Health, Novartis, American College of Chest Physicians, Projects in Knowledge, Hybrid Communications, Medscape, Ultimate Medical Academy, Eastern Pulmonary Society, Catamount Medical, Eastern VA Medical Center, Academy Continued Health Care Learning and Wolters Kluwer Health, grants from Pearl Research and NHLBI, other (advisory board) from Verona, Boehringer Ingelheim, Theravance and Science 24/7, non-financial support and other (advisory board) from Circassia and Phillips, personal fees and non-financial support for consultancy from Third Pole, non-financial support and other (data monitoring committee) from Shire, and personal fees for data monitoring committee work from Takeda, outside the submitted work. I.D. Pavord reports personal fees for lectures, advisory board work, meeting attendance and organising educational events from AstraZeneca, personal fees for lectures, advisory board work and meeting attendance from Boehringer Ingelheim and GlaxoSmithKline, personal fees for lectures from Aerocrine and Chiesi, personal fees for lectures and advisory board work from Almirall and Novartis, personal fees for advisory board work from Genentech, Regeneron, Sanofi, Circassia and Knopp, personal fees for lectures, meeting attendance and organising educational events from Teva, and grants from NIHR, outside the submitted work. D. Price reports study funding from AstraZeneca, during the conduct of the study; personal fees for advisory board work and consultancy from Amgen, grants and personal fees for advisory board work, lectures, consultancy and travel/accommodation/meeting expenses from AstraZeneca and Boehringer Ingelheim, grants and personal fees for advisory board work, lectures and consultancy from Chiesi, Mylan and Teva, grants and personal fees for advisory board work from Circassia, personal fees for lectures from Cipla and Kyorin, personal fees for consultancy and lectures from GlaxoSmithKline, grants and personal fees for advisory board work, lectures, consultancy, travel/accommodation/meeting expenses and educational activities from Mundipharma and Novartis, grants and personal fees for consultancy from Pfizer and Theravance, grants and personal fees for advisory board work and lectures from Regeneron Pharmaceuticals and Sanofi Genzyme, grants from Respiratory Effectiveness Group and UK National Health Service, personal fees for advisory board work and travel/accommodation/meeting expenses from ThermoFisher, non-financial support for grant committee reviewing from Efficacy and Evaluation Mechanism Programme and Health Technology Assessment, outside the submitted work; has stock/stock options from AKL Research and Development Ltd which produces phytopharmaceuticals; and is part owner of the social enterprise Optimum Patient Care Ltd (Australia and UK) and of the Observational and Pragmatic Research Institute

Pte Ltd (Singapore). E. Rapsomaniki is an employee of AstraZeneca (UK). N. Karlsson is an employee of AstraZeneca. D.K. Finch was an employee of AstraZeneca at the time of authorship. J. Nuevo is an employee of AstraZeneca. A. de Giorgio-Miller has nothing to disclose. M. Alacqua has nothing to disclose. R. Hughes reports personal fees from GlaxoSmithKline, Novartis, Boehringer Ingelheim and AstraZeneca, outside the submitted work; and is an employee of AstraZeneca. H. Müllerová is an employee of AstraZeneca. M. Gerhardsson de Verdier is an employee of AstraZeneca.

Support statement: The NOVELTY study is funded by AstraZeneca.

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