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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>

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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 (novelystudy.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 ($\text{FEF}_{25-75\%}$), 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 ≥ 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).

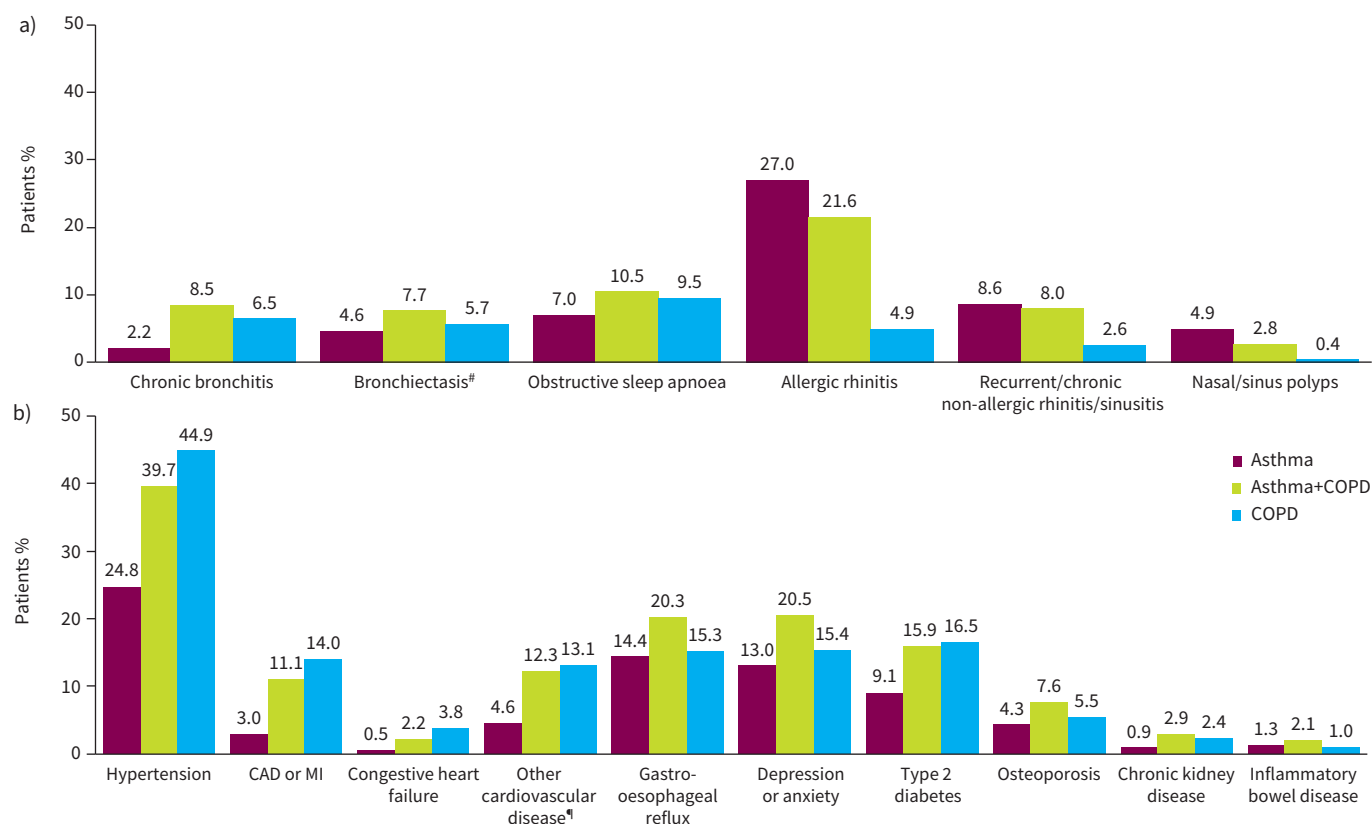


FIGURE 1 a) Respiratory and b) non-respiratory comorbidities in the NOVELTY population, by physician-assigned diagnosis. COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; MI: myocardial infarction. [#]: from an electronic case report form entry under “Respiratory Comorbidities” 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

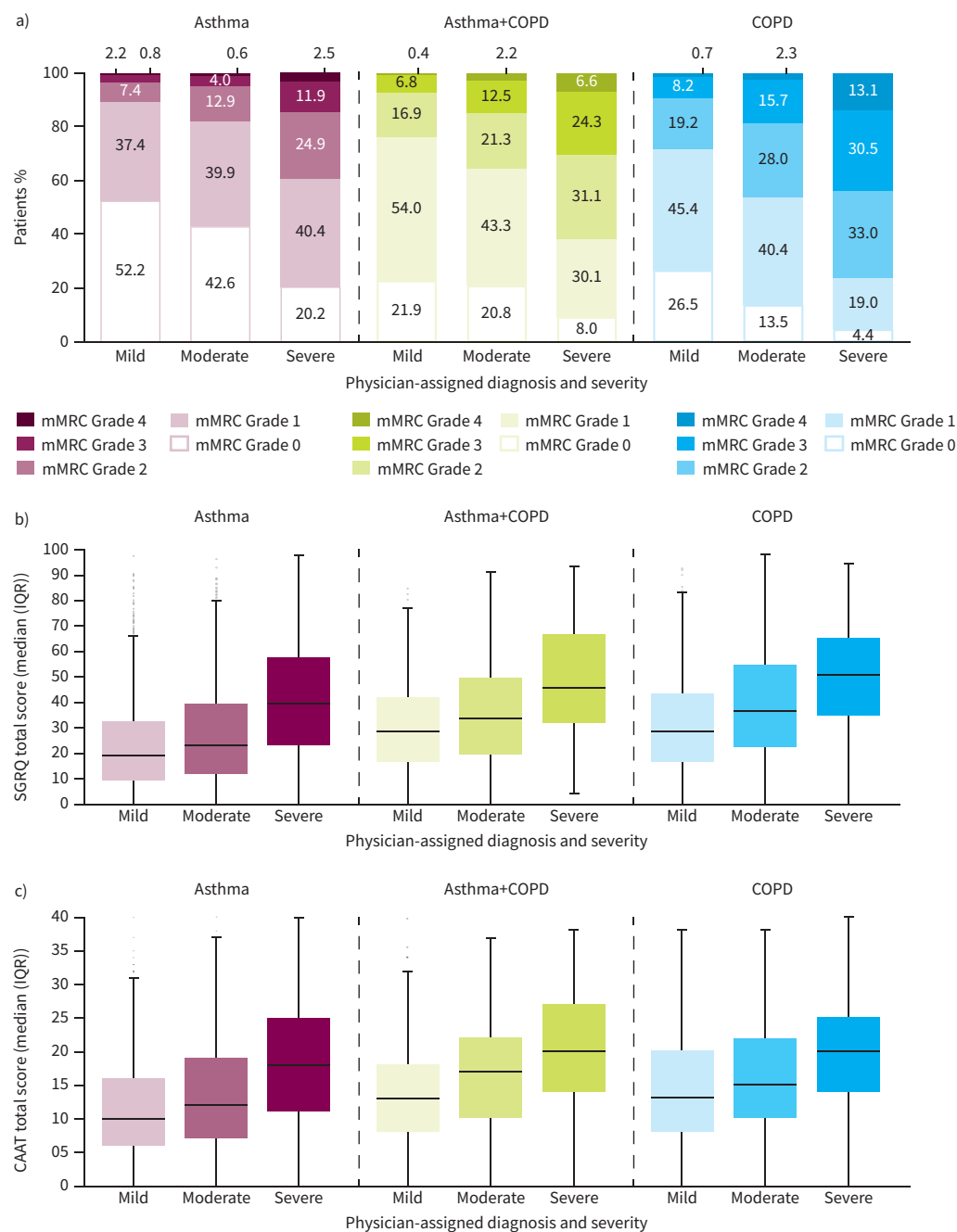


FIGURE 2 Variability in **a)** modified Medical Research Council (mMRC) dyspnoea grade (available for 96.5% of patients), **b)** St George's Respiratory Questionnaire (SGRQ) total score (available for 69.3% of patients) and **c)** Chronic Airways Assessment Test (CAAT[®]) total score (available for 70.0% 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 FEV₁ % 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 FEV₁/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; FEV₁: 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?”

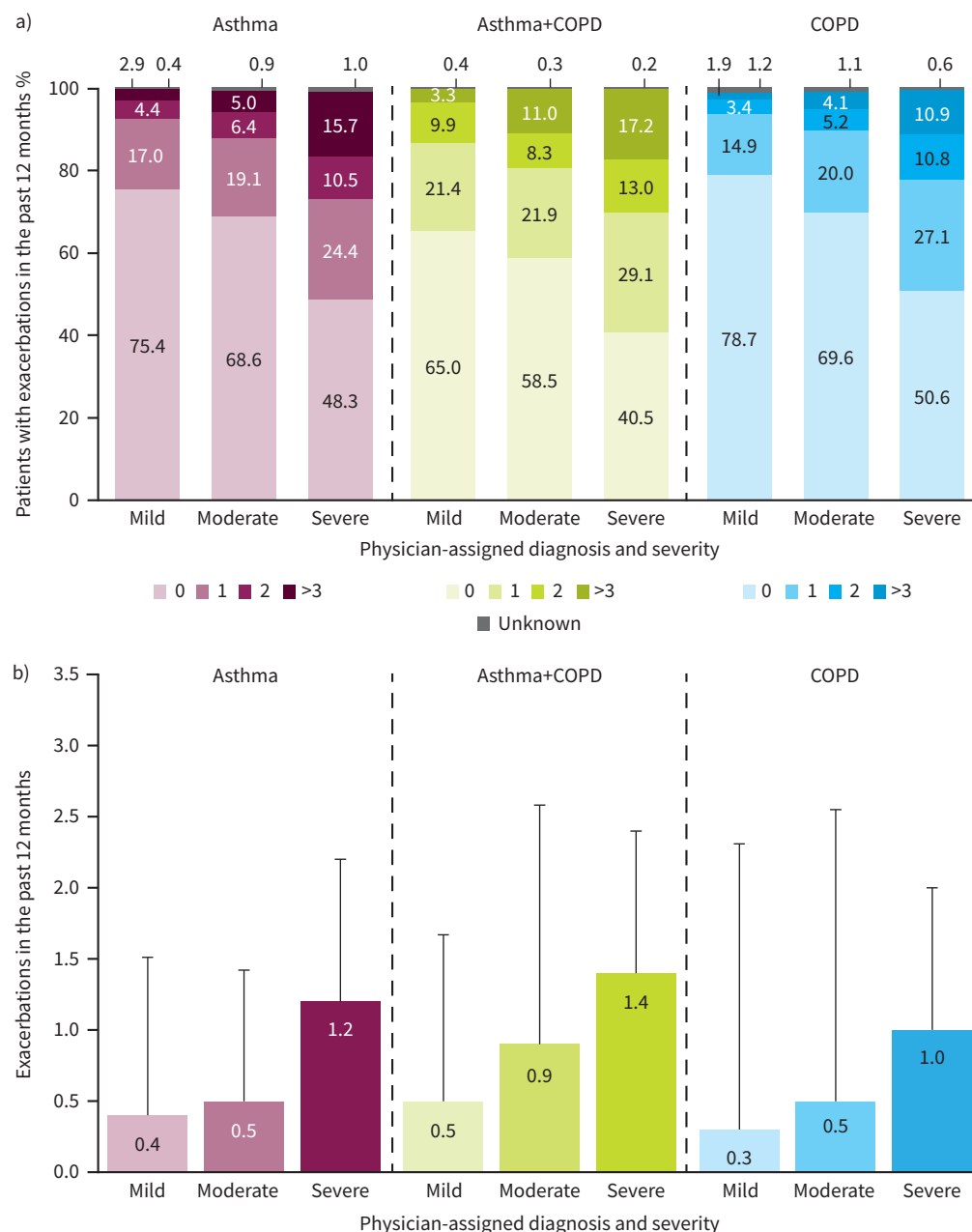


FIGURE 3 Frequency distribution by **a)** the number of exacerbations[#] and **b)** the mean number of exacerbations (among all patients, including those with no exacerbations) in the past 12 months, by physician-assigned diagnosis and severity.[¶] In **b**, data are presented as mean+SD. COPD: chronic 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 FEV₁/FVC and FEV₁ 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).

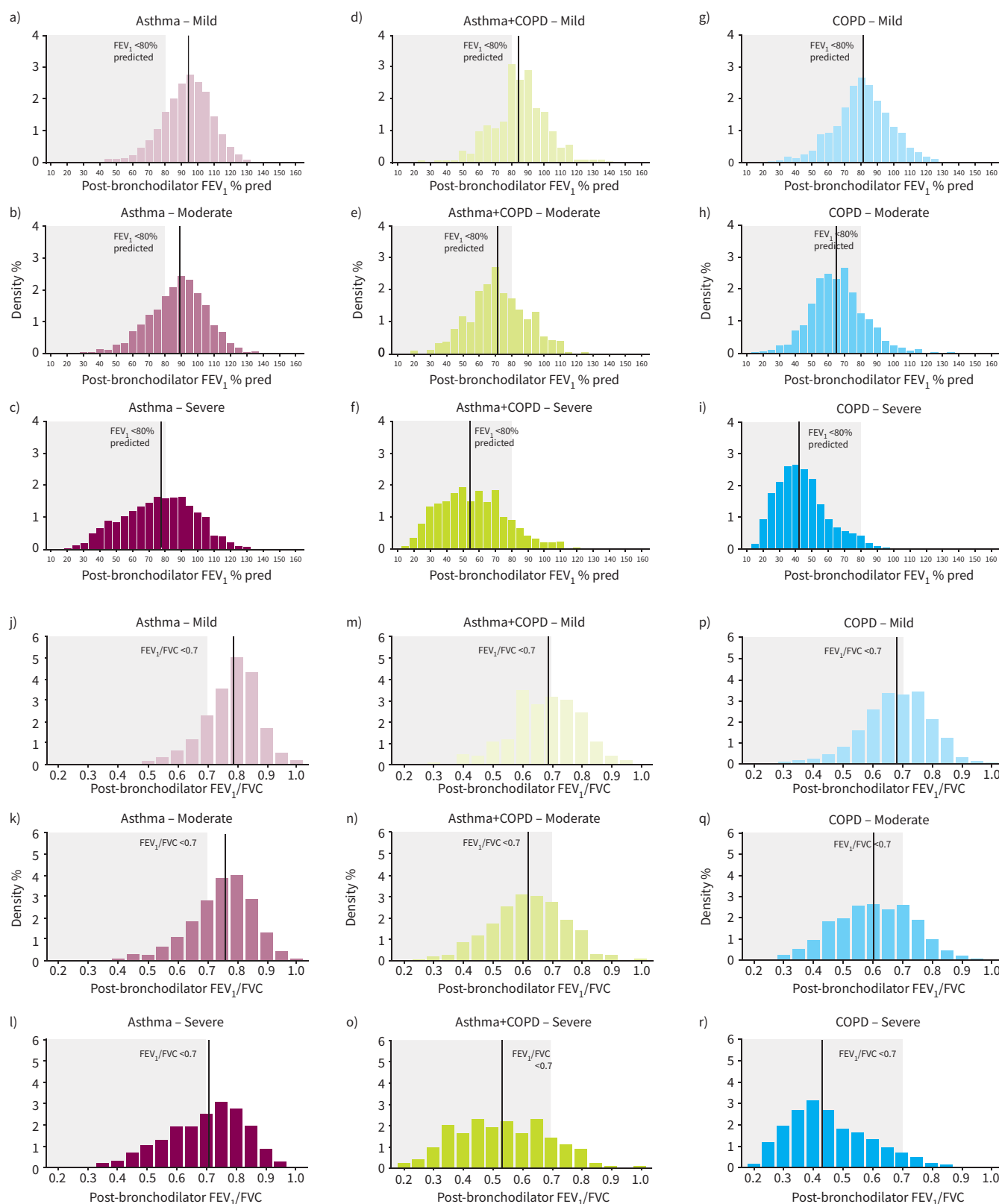


FIGURE 4 Heterogeneity in a–i) post-bronchodilator forced expiratory volume in 1 s (FEV_1), j–r) post-bronchodilator FEV_1 /forced vital capacity (FVC) and s–aa) bronchodilator responsiveness, by physician-assigned diagnosis and severity. For continuous data, density is calculated as frequency divided 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].

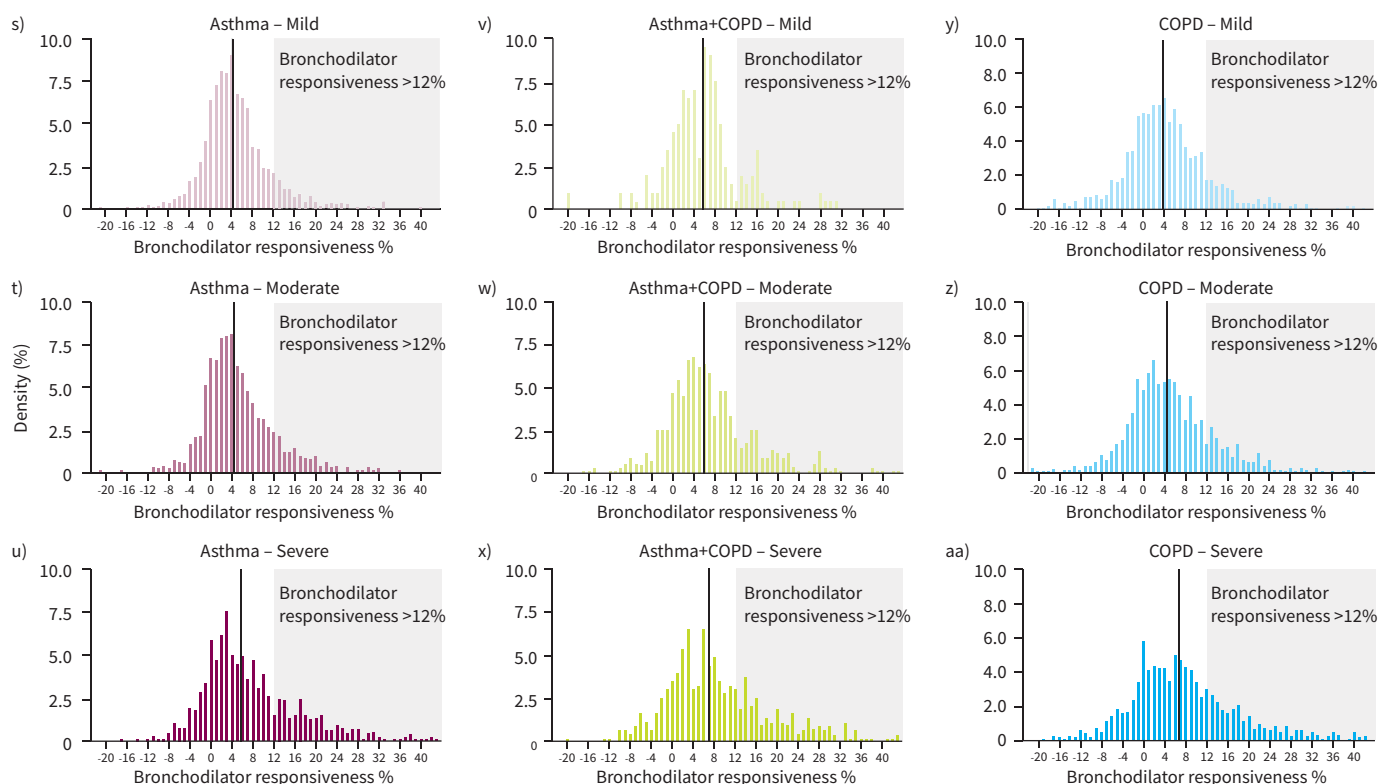


FIGURE 4 Continued.

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 10⁹·μL⁻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 10⁹·μL⁻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 β₂-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.

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