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

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Take home message: Heterogeneity within and between patients with physician-assigned diagnoses of asthma and/or COPD in the NOVELTY cohort at baseline suggests that current diagnostic and severity classifications poorly differentiate between clinically important phenotypes

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, 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 11243 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 post-bronchodilator FEV_1/FVC <lower limit of normal.

Symptoms and exacerbations increased with greater physician-assessed severity, and were higher in asthma+COPD, but 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/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.

ClinicalTrials.gov identifier: NCT02760329.

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 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 sub-groups (*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 include 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 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 describe the baseline clinical, physiological and biomarker characteristics of the global NOVELTY population.

Methods

Study design

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 (*e.g.* 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 (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 were considered unlikely to complete 3 years' follow-up. To ensure sufficient numbers for regional or sub-group

analyses, sampling was stratified by diagnosis (asthma, asthma+COPD, COPD) and by physician-assessed severity (mild, moderate, severe); enrolment was capped in some sub-groups 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 (FeNO) level (Supplement); pre- and post-bronchodilator forced expiratory volume in 1 second (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 hours and long-acting bronchodilators for 12–24 hours 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)/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/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 (table S2). Data for patients from China were excluded from the present analyses due 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 (Supplement). 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.

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; 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 (table S3).

Heterogeneity and overlap by physician-assigned diagnosis

At baseline, 5940 (52.8%) patients 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% (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 (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).

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 *versus* COPD, whereas cardiovascular comorbidities were more prevalent among patients with asthma+COPD or COPD *versus* 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 FeNO was lower among never or former smokers with COPD, *versus* asthma (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 $\geq$30.0 kg/m^2); obesity was less common among patients with severe COPD than severe asthma/asthma+COPD. Current smoking was less common in patients with severe COPD than in 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).

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 (figure S2, table S5) and diagnosis/severity group (figure 2, figure S3, 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, 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 (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, figures S2–S3). Lung function was 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, tables S4–S5 and figures S2–S3).

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

The distribution of bronchodilator responsiveness (available for 80.3% [n=9034] of patients) overlapped across physician-assigned diagnosis and severity groups (figures S2–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 (table S5). Among patients with asthma or asthma+COPD, bronchodilator responsiveness increased with increasing physician-assessed severity (table 2, 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 mild asthma were most commonly receiving medium/high-dose inhaled corticosteroid long-acting β_2-agonist (ICS-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 long-acting bronchodilators (LABA and/or long-acting muscarinic antagonist [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 (table S6).

Biomarkers

There was little variation in blood eosinophil counts by severity, even after excluding patients taking maintenance OCS or anti-IL5 therapy, but blood neutrophil counts increased with physician-assessed severity across all diagnoses; there were no clear patterns for eosinophil and neutrophil percentages by severity (table 3). Levels of FeNO 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 (figure S4A). Notably, current smoking was associated with *lower* severity classification than never/former smoking; obesity was also independently associated with lower severity. Figure

S4 also shows significant factors for asthma and COPD separately. Results of the univariate analysis are shown in 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 sub-groups of patients. This indicates that the historical labels of 'asthma' and 'COPD' and the severity classifications used in clinical practice, do not identify clinically distinctive 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, as 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 on 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 focussed on selected populations with either diagnosis, based on conventional criteria, from a particular care

setting or geographic region, or focussing 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 asthma and 13.1% of patients labelled as 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, and smoking and emphysema, that are commonly associated with asthma[23] and COPD[24], respectively, 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 neutrophils 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 over-simplified 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, whilst 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 have reported that some patients with mild asthma (defined by treatment level) experience severe exacerbations[34, 35], 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 sub-group 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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Tables

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

	Asthma (N=5940)*	**Asthma+COPD (N=1396)***	**COPD (N=3907)***	**Total (N=11,243)***
Sex, n (%) female	3714 (62.5)	655 (46.9)	1506 (38.5)	5875 (52.3)
Age (years), mean ± SD	52.0 ± 17.1	64.7 ± 10.3	66.6 ± 9.6	58.7 ± 15.8
Ethnicity, n (%)				
N with data	5925	1396	3907	11228
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 (%)				
N with data	5917	1390	3894	11201
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, mean ± SD				
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, n (%)	1487 (25.0)	293 (21.0)	176 (4.5)	1956 (17.4)
Family history, n (%)				
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 (%)[‡]				
N with data	5935	1392	3905	11232
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)

For percentages, the denominator is given when different from the total number of patients (N with data [excluding 'unknown']). COPD: chronic obstructive pulmonary disease; n: number of patients in the specified category; N: total number of patients; NA: not applicable; SD: standard deviation. [*]>90% of patients had complete data for variables in table 1. [†]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 is the worse of the two physician-assessed severity classifications. 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.

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 (N=2175)†	**Moderate (N=2108)†**	**Severe (N=1652)†**	**Mild (N=243)†**	**Moderate (N=626)†**	**Severe (N=523)†**	**Mild (N=1125)†**	**Moderate (N=1206)†**	**Severe (N=1574)†**
Sex, n (%) female	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), mean ± SD	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), mean ± SD	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 kg/m^2, n (%)	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 kg/m^2, n (%)	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 kg/m^2, n (%)	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 kg/m^2, n (%)	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 (%)									
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, n (%)	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, n (%)	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, n (%)	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, n (% of those with allergy testing)	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, n (%)	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 (% of patients with non-missing data)‡									
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)

	Physician-assigned asthma			Physician-assigned asthma+COPD			Physician-assigned COPD		
	Mild (N=2175)†	**Moderate (N=2108)†**	**Severe (N=1652)†**	**Mild (N=243)†**	**Moderate (N=626)†**	**Severe (N=523)†**	**Mild (N=1125)†**	**Moderate (N=1206)†**	**Severe (N=1574)†**
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, mean ±SD§	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, mean ±SD§	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, n (%)	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, n (%)	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 (%), mean ± SD	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, n (%)	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, mean ± SD**	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, n (%)	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, n (%)	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 (%)									
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)

For percentages, the denominator is given when different from the total number of patients (N with data [excluding 'unknown']). BMI: body mass index; COPD: chronic obstructive pulmonary disease; eCRF: electronic case report form; FEV_1: forced expiratory volume in 1 second; FVC:

forced vital capacity; n: number of patients in the specified category; LLN: lower limit of normal; N: total number of patients; NA: not applicable; PRO: patient-reported outcome; SD: standard deviation; SGRQ: St George's Respiratory Questionnaire. [*]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. Patients with COPD classified as 'very severe' were included in the 'severe' group. [†]Approximately 80% of patients had post-bronchodilator spirometry data, 70% had PRO data and >90% had complete data for other variables. [‡]From the question that precedes the SGRQ: "*please tick in one box to show how you describe your current health"*. [§]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 eCRF: *"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?"*

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 (N=2175)†	**Moderate (N=2108)†**	**Severe (N=1652)†**	**Mild (N=243)†**	**Moderate (N=626)†**	**Severe (N=523)†**	**Mild (N=1125)†**	**Moderate (N=1206)†**	**Severe (N=1574)†**
Respiratory medications, n (%)‡									
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**	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/μL) geo mean ± geo SD	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-IL-5/5R	917	839	600	126	325	257	471	515	730
Excluding patients with OCS, anti-IL-4/4R or anti-IL-5/5R	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), geo mean ± geo SD	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-IL-5/5R	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/μL),	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

	Physician-assigned asthma			Physician-assigned asthma+COPD			Physician-assigned COPD		
	Mild (N=2175)†	**Moderate (N=2108)†**	**Severe (N=1652)†**	**Mild (N=243)†**	**Moderate (N=626)†**	**Severe (N=523)†**	**Mild (N=1125)†**	**Moderate (N=1206)†**	**Severe (N=1574)†**
geo mean ± geo SD									
Blood neutrophil proportion (% of total leukocytes), geo mean ± geo SD	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
FeNO (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)

For percentages, the denominator is given when different from the total number of patients (N with data [excluding 'unknown']). BD: bronchodilator; COPD: chronic obstructive pulmonary disease; FeNO: fractional exhaled nitric oxide; Geo: geometric; ICS: inhaled corticosteroid; IL-4/4R: interleukin-4 or interleukin-4 receptor; IL-5/5R: interleukin-5 or interleukin-5 receptor; IQR: interquartile range; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; med: medium; n: number of patients in the specified category; N: total number of patients; OCS: oral corticosteroid. *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. Patients with COPD classified as 'very severe' were included in the 'severe' group. †Approximately 50% of patients had biomarker data. ‡Medications categories are defined in table S2. ICS dose was classified according to Global Initiative for Asthma 2019 definition[37]. §'No ICS' was defined as neither maintenance nor reliever ICS; **Without maintenance OCS or biologic therapy.

Figure legends

FIGURE 1 Respiratory (A) and non-respiratory (B) comorbidities in the NOVELTY population, by physician-assigned diagnosis.

CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; eCRF: electronic case report form; MI: myocardial infarction. *From an eCRF entry under 'Respiratory Comorbidities' and/or from a record of abnormal computed tomography findings. †Any cardiovascular disease other than hypertension, coronary artery disease, myocardial infarction or congestive heart failure.

FIGURE 2 Variability in mMRC dyspnoea grade* (A) SGRQ total score† (B) and CAAT total score‡ (C) by physician-assigned diagnosis and severity§.

For panels B and C, boxes are median (IQR [Q1–Q3]); whiskers extend to 1.5 times the IQR, with circles representing individual outliers. CAAT: Chronic Airways Assessment Test; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; mMRC: modified Medical Research Council; SGRQ: St George's Respiratory Questionnaire. *mMRC dyspnoea scale data were available for 96.5% of patients. †SGRQ data were available for 69.3% of patients. ‡CAAT data were available for 70.0% of patients; 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. Patients with COPD classified as 'very severe' were included in the 'severe' group.

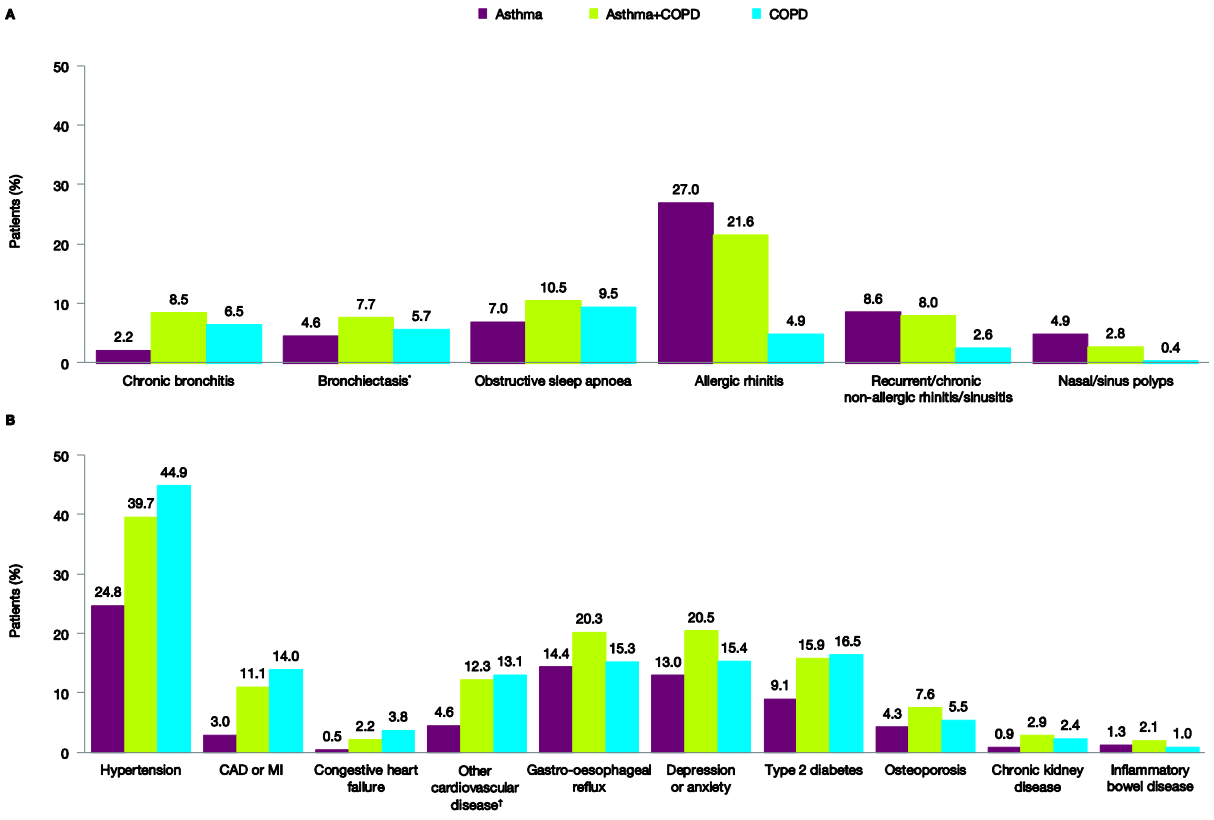
FIGURE 3 Frequency distribution by the number of exacerbations (A) and the mean number of exacerbations* (B) in the past 12 months, by physician-assigned diagnosis and severity†.

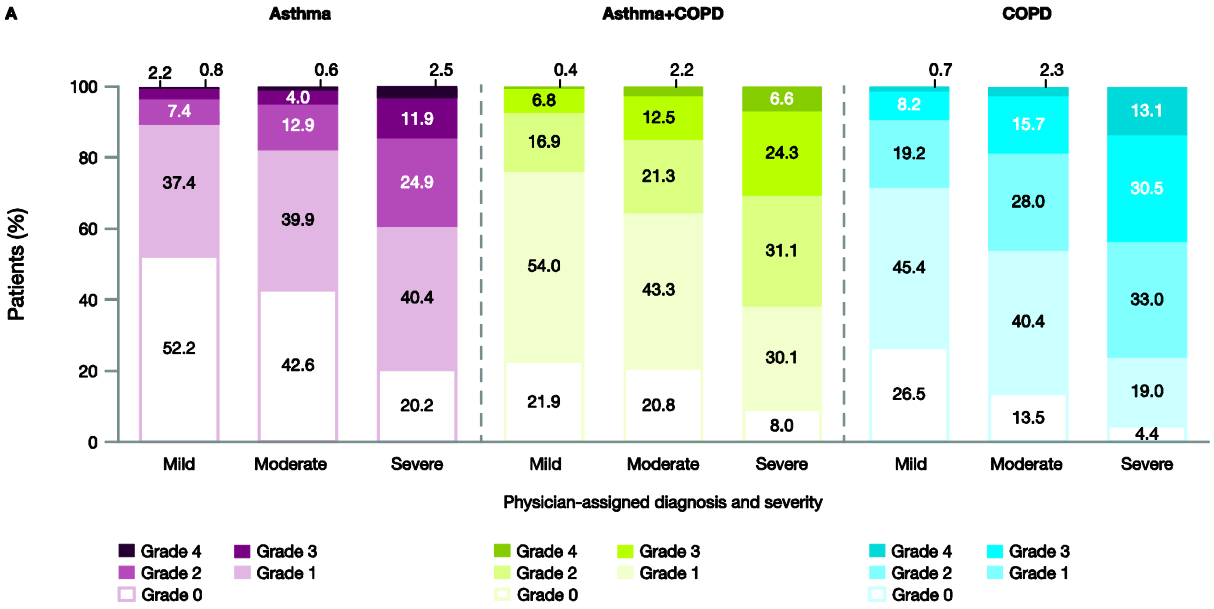
COPD: chronic obstructive pulmonary disease; eCRF: electronic case report form; SD: standard deviation. *Among all patients, including those with no exacerbations. Exacerbations include mild, moderate and severe exacerbations, from the following question in the eCRF: *"During the past 12 months, on how 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. Patients with COPD classified as 'very severe' were included in the 'severe' group.

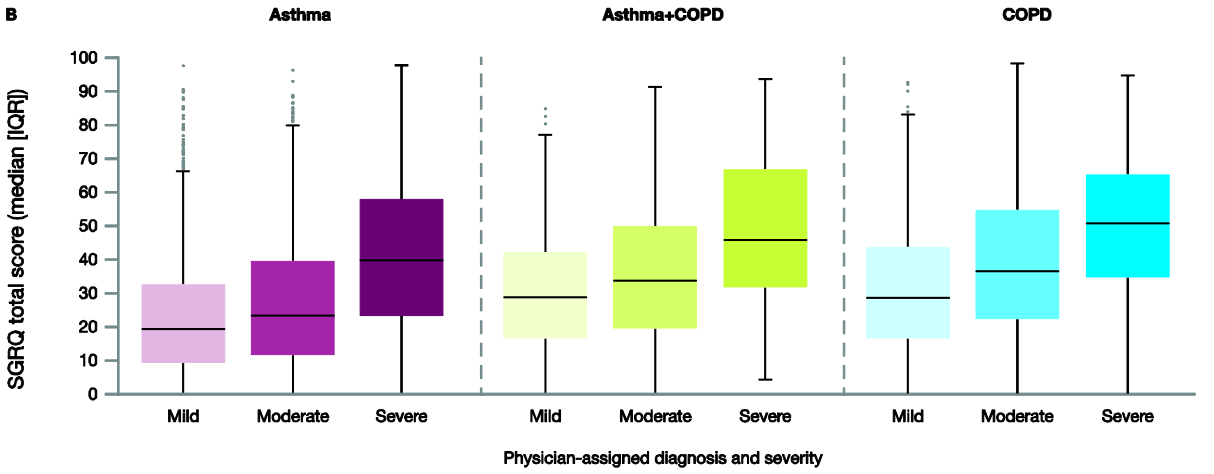
FIGURE 4 Heterogeneity in (A) post-bronchodilator FEV_1, (B) post-bronchodilator FEV_1/FVC, and (C) bronchodilator responsiveness, by physician-assigned diagnosis and severity.

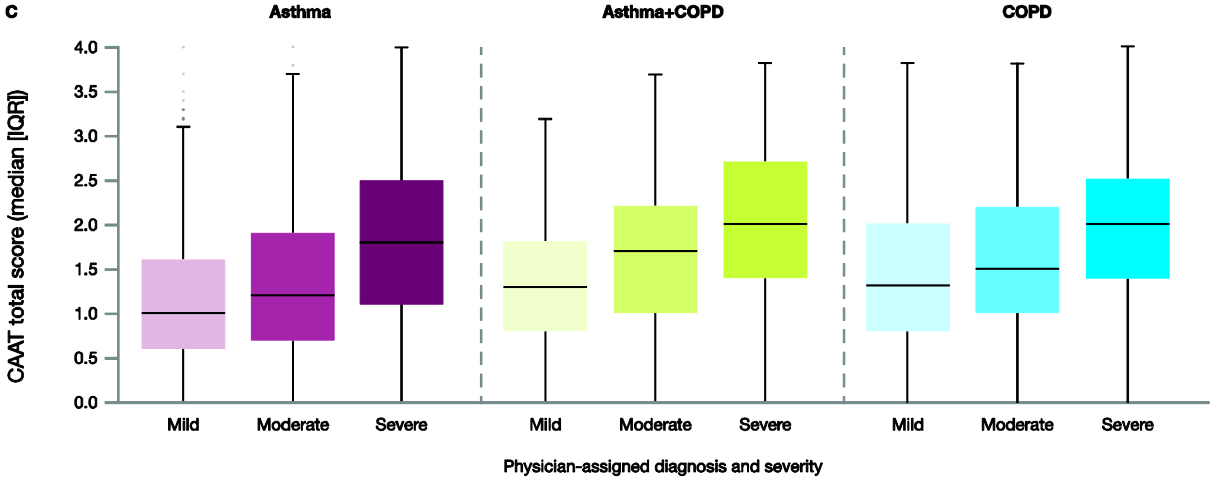
For continuous data, density is calculated as frequency divided by category width. The solid black lines show the median values. Grey shading shows the spirometric thresholds used in asthma/COPD diagnostic criteria[2, 3]. See table S3 for the number of patients with post-bronchodilator spirometry data. Global Lung Function Initiative multi-ethnic reference

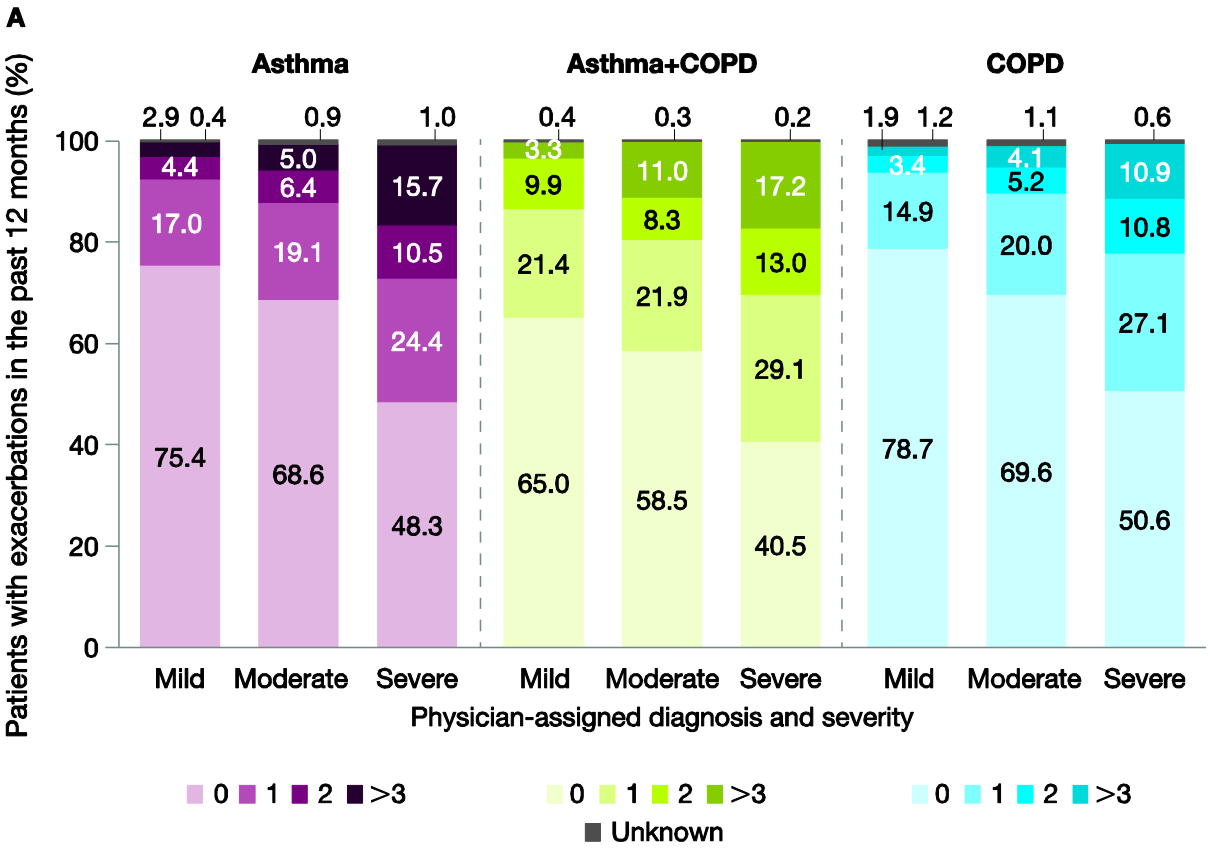
equations were used to calculate % predicted values[13]. COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity.

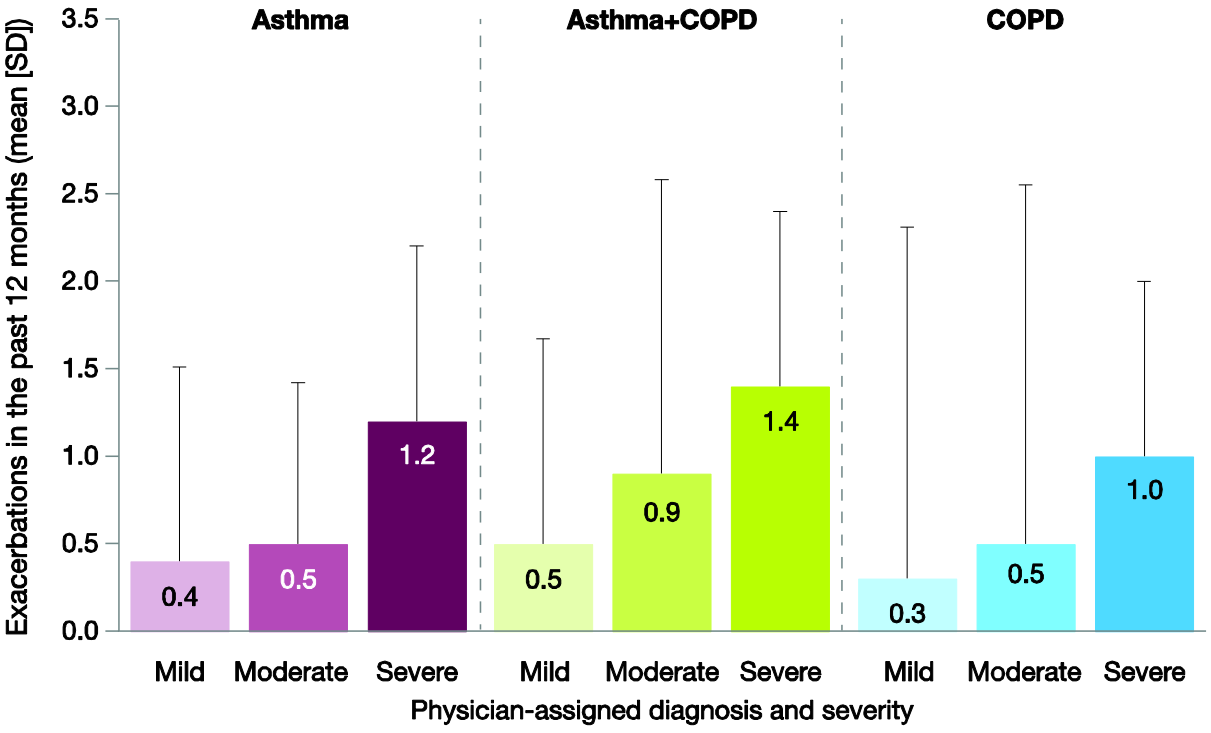

A
Asthma
Asthma+COPD
COPD
Patients (%)
50
40
30
20
10
0
2.2
8.5
6.5
4.6
7.7
5.7
7.0
10.5
9.5
27.0
21.6
4.9
8.6
8.0
2.6
4.9
2.8
0.4
Chronic bronchitis
Bronchiectasis*
Obstructive sleep apnoea
Allergic rhinitis
Recurrent/chronic non-allergic rhinitis/sinusitis
Nasal/sinus polyps
B
Patients (%)
50
40
30
20
10
0
24.8
39.7
44.9
3.0
11.1
14.0
0.5
2.2
3.8
4.6
12.3
13.1
14.4
20.3
15.3
13.0
20.5
15.4
9.1
15.9
16.5
4.3
7.6
5.5
0.9
2.9
2.4
1.3
2.1
1.0
Hypertension
CAD or MI
Congestive heart failure
Other cardiovascular disease†
Gastro-oesophageal reflux
Depression or anxiety
Type 2 diabetes
Osteoporosis
Chronic kidney disease
Inflammatory bowel disease

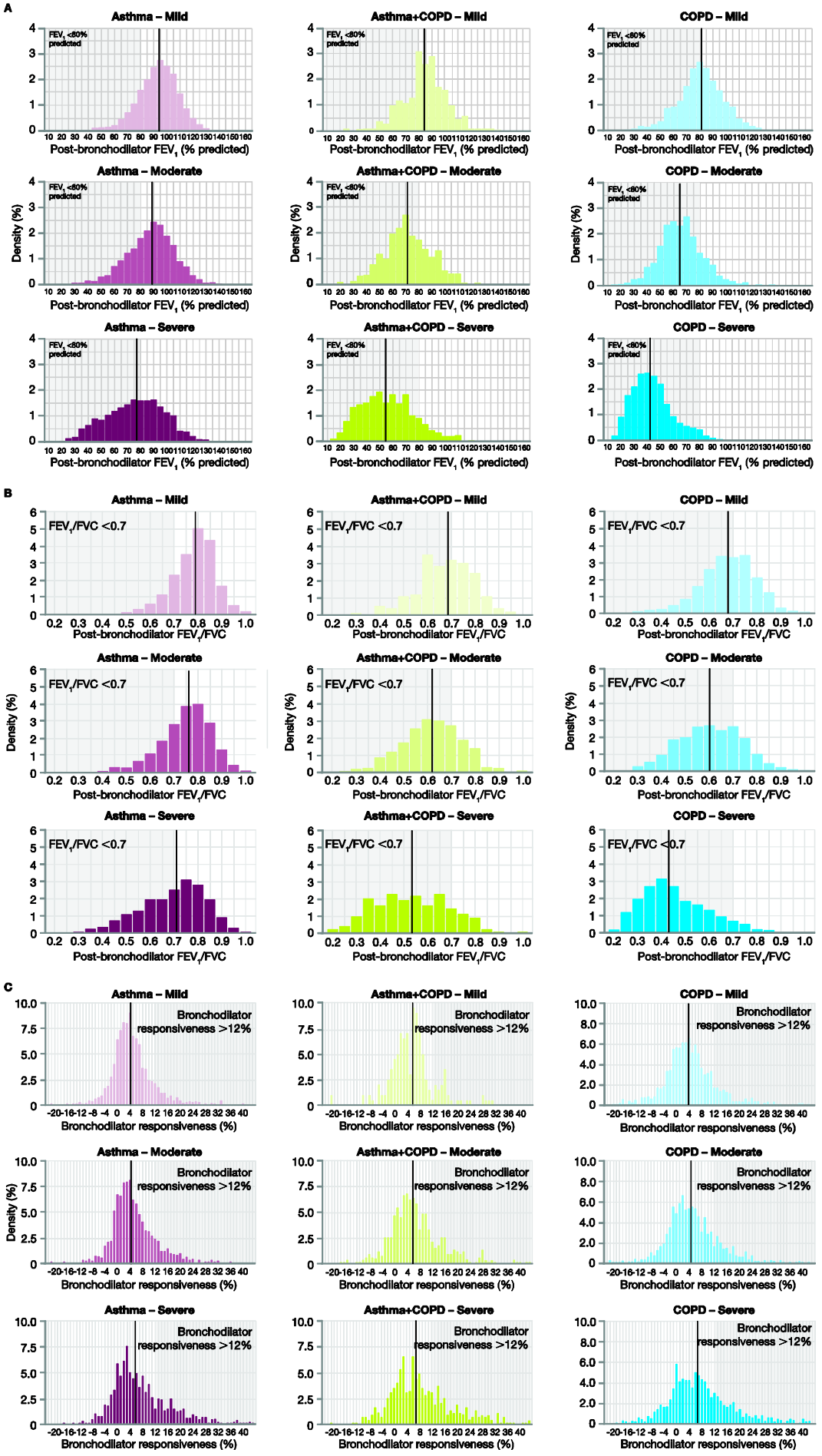

A
Asthma
Asthma+COPD
COPD
Patients (%)
2.2
0.8
0.6
2.5
0.4
2.2
0.7
2.3
7.4
37.4
52.2
4.0
12.9
39.9
42.6
11.9
24.9
40.4
20.2
6.8
16.9
54.0
21.9
12.5
21.3
43.3
20.8
6.6
24.3
31.1
30.1
8.0
8.2
19.2
45.4
26.5
15.7
28.0
40.4
13.5
13.1
30.5
33.0
19.0
4.4
Mild
Moderate
Severe
Physician-assigned diagnosis and severity
Grade 4
Grade 3
Grade 2
Grade 1
Grade 0


B
Asthma
Asthma+COPD
COPD
SGRQ total score (median [IQR])
Mild
Moderate
Severe
Physician-assigned diagnosis and severity


C
Asthma
Asthma+COPD
COPD
CAAT total score (median [IQR])
Mild
Moderate
Severe
Physician-assigned diagnosis and severity


A
Asthma
Asthma+COPD
COPD
Patients with exacerbations in the past 12 months (%)
2.9 0.4
0.9
1.0
0.4
0.3
0.2
1.9 1.2
1.1
0.6
4.4
17.0
75.4
5.0
6.4
19.1
68.6
15.7
10.5
24.4
48.3
3.3
9.9
21.4
65.0
11.0
8.3
21.9
58.5
17.2
13.0
29.1
40.5
3.4
14.9
78.7
4.1
5.2
20.0
69.6
10.9
10.8
27.1
50.6
Mild
Moderate
Severe
Physician-assigned diagnosis and severity
0 1 2 >3
Unknown


B
Asthma
Asthma+COPD
COPD
Exacerbations in the past 12 months (mean [SD])
0.4
0.5
1.2
0.5
0.9
1.4
0.3
0.5
1.0
Mild
Moderate
Severe
Physician-assigned diagnosis and severity


A
Asthma – Mild
Asthma+COPD – Mild
COPD – Mild
Asthma – Moderate
Asthma+COPD – Moderate
COPD – Moderate
Asthma – Severe
Asthma+COPD – Severe
COPD – Severe
FEV1 <80% predicted
Density (%)
Post-bronchodilator FEV1 (% predicted)
B
FEV1/FVC <0.7
Post-bronchodilator FEV1/FVC
C
Bronchodilator responsiveness >12%
Bronchodilator responsiveness (%)

Supplementary material

Fractional exhaled nitric oxide measurement

Fractional exhaled nitric oxide (FeNO) was measured locally by site personnel according to the recommendation of the equipment manufacturer and the ATS/ERS recommendations [1]. Sites that did not have suitable FeNO equipment were provided with a Niox Vero device (Circassia, Oxford, UK) for the duration of the study. At baseline, 77% of patients were from sites using a Niox Vero device.

Covariates for multivariable ordinal regression models

Selection of covariates for the multivariable ordinal logistic regression models to identify factors associated with physician-assigned severity (mild, moderate and severe/very severe [pooled]) was guided by outputs from univariate ordinal regression models adjusted for age at baseline ($p<0.2$; figure S4), and by clinical relevance, with removal of variables that were known to be overlapping or considered to be highly correlated. Comorbidities were recorded in the electronic case report by selecting from a checklist rather than by yes/no responses; therefore, non-recording of a comorbidity may include both 'not present' and 'not known'. The resulting list of covariates included in the multivariable models was: age, body mass index, smoking status, modified Medical Research Council dyspnoea scale grade, time since diagnosis of asthma or chronic obstructive pulmonary disease, exacerbations in the past 12 months, post-bronchodilator forced expiratory volume in 1 second (FEV_1) % predicted, post-bronchodilator FEV_1/forced vital capacity, bronchodilator responsiveness, allergic rhinitis, non-allergic rhinitis, nasal or sinus polyps, and diagnosis of emphysema. The selected variables were entered into ordinal regression models fitted for asthma and COPD separately,

and overall (excluding patients with asthma+COPD).

Supplementary tables and figures

TABLE S1 Patients included in the baseline analysis, by country

	Number (%) of patients (N=11243)
Argentina*	521 (4.6)
Australia	818 (7.3)
Brazil*	202 (1.8)
Canada*	1178 (10.5)
Colombia	252 (2.2)
Denmark	97 (0.9)
France*	747 (6.6)
Germany*	774 (6.9)
Italy*	590 (5.2)
Japan	820 (7.3)
Mexico*	143 (1.3)
The Netherlands	318 (2.8)
Norway*	52 (0.5)
South Korea	606 (5.4)
Spain*	975 (8.7)
Sweden	335 (3.0)
UK*	894 (8.0)
USA*	1921 (17.1)

Patients enrolled between 25 July 2016 and 5 March 2018 were included in the baseline analysis. In China, after a later start to recruitment, a total of 47 patients were enrolled by 5 March 2018 but were excluded from the baseline analysis due to a change in regulations about data transfer in May 2019. All countries recruited patients ≥18 years of age. *Recruited patients ≥12–<18 years of age in addition to patients ≥18 years of age. See Table S7 for a list of study investigators in each country. N: total number of patients.

TABLE S2 Medication categories

Label	Must have	Must not have	Allowed
No ICS	-	Any ICS-containing inhaler (maintenance or reliever)	All
Short-acting BD, no ICS	SABA and/or SAMA	Any ICS-containing inhaler (maintenance or reliever), LABA, LAMA, maintenance OCS, biologic therapy	Other respiratory medications
Any ICS	Any ICS-containing inhaler (maintenance and/or reliever)	-	All
LABA and/or LAMA, no ICS	LABA and/or LAMA	Any ICS-containing inhaler (maintenance or reliever), maintenance OCS, biologic therapy	Any non-ICS-containing reliever, other respiratory medications
Low-dose ICS	ICS low-dose*	LABA and/or LAMA, maintenance OCS, biologic therapy	Any reliever (including ICS-containing), other respiratory medications
Low-dose ICS+LABA	ICS low-dose* + LABA (separate or in combination)	LAMA, maintenance OCS, biologic therapy	Any reliever (including ICS-containing), other respiratory medications
Med/high-dose ICS+LABA	ICS medium or high-dose*	LABA and/or LAMA, maintenance OCS, biologic therapy	Any reliever (including ICS-containing), other respiratory medications
ICS+LABA+LAMA	ICS+LAMA+LABA (separate or combination)	Maintenance OCS, biologic therapy	Any reliever (including ICS-containing), other respiratory medications
Maintenance OCS	OCS (or injected corticosteroid) in the maintenance treatment section of the eCRF	-	All
Biologic therapy	Anti-IgE, anti-IL5/5R, anti-IL4	-	All
Leukotriene modifier	LTRA and/or 5-LO inhibitor	-	All

Other respiratory medications	Leukotriene modifier, methylxanthine, long-term antibiotics and/or PDE4 inhibitor	-	All

*ICS dose was classified according to the Global Initiative for Asthma 2019 definitions [2].

5-LO: 5-lipoxygenase; BD: bronchodilator; ICS: inhaled corticosteroid; IL: interleukin; IgE: immunoglobulin E; LABA: long-acting β2-agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; med: medium; n: number of patients in the specified category; N: total number of patients; OCS: oral corticosteroid; PDE4: phosphodiesterase 4; R: receptor.

TABLE S3 Demographics, disease history and clinical characteristics of the NOVELTY population, overall and by recruitment setting*

	Overall (N=11,243)	**Primary care (N=5247)**	**All non-primary care† (N=5996)**	**University hospital (N=3005)**	**Research facility (N=1331)**	**Non-university hospital (N=979)**	**Specialists (N=493)**	**Private practice (N=90)**
Physician-assigned diagnosis of asthma, n (%)‡	5940 (52.8)	2813 (53.6)	3127 (52.2)	1689 (56.2)	621 (46.7)	473 (48.3)	235 (47.7)	40 (44.4)
Mild	2175 (19.4)	1117 (21.3)	1058 (17.7)	518 (17.2)	280 (21.0)	153 (15.6)	70 (14.2)	14 (15.6)
Moderate	2108 (18.8)	1045 (20.0)	1063 (17.7)	548 (18.2)	219 (16.5)	127 (13.0)	140 (28.4)	15 (16.7)
Severe	1652 (14.7)	646 (12.3)	1006 (16.8)	623 (20.7)	122 (9.2)	193 (19.7)	25 (5.1)	11 (12.2)
Physician-assigned diagnosis of asthma+COPD, n (%)‡	1396 (12.4)	641 (12.2)	755 (12.6)	316 (10.5)	227 (17.1)	135 (13.8)	54 (11.0)	13 (14.4)
Mild	243 (2.2)	118 (2.3)	125 (2.1)	40 (1.3)	50 (3.8)	27 (2.8)	5 (1.0)	2 (2.2)
Moderate	626 (5.6)	283 (5.4)	343 (5.7)	146 (4.9)	106 (8.0)	53 (5.4)	28 (5.7)	6 (6.7)
Severe	523 (4.7)	238 (4.5)	285 (4.8)	129 (4.3)	71 (5.3)	54 (5.5)	21 (4.3)	5 (5.6)
Physician-assigned diagnosis of COPD, n (%)‡	3907 (34.7)	1793 (34.2)	2114 (35.3)	1000 (33.3)	483 (36.3)	371 (37.9)	204 (41.4)	37 (41.1)
Mild	1125 (10.0)	459 (8.8)	666 (11.1)	283 (9.4)	208 (15.6)	90 (9.2)	77 (15.6)	6 (6.7)
Moderate	1206 (10.7)	580 (11.1)	626 (10.4)	306 (10.2)	132 (9.9)	77 (7.9)	87 (17.6)	13 (14.4)
Severe	1574 (14.0)	752 (14.4)	822 (13.7)	411 (13.7)	143 (10.7)	204 (20.8)	40 (8.1)	18 (20.0)
Sex, n (%) female	5875 (52.3)	2876 (54.8)	2999 (50.0)	1422 (47.3)	760 (57.1)	457 (46.7)	261 (52.9)	47 (52.2)
Age (years), mean ± SD	58.7 ± 15.8	58.5 ± 16.1	58.8 ± 15.5	58.2 ± 15.7	60.3 ± 14.8	60.8 ± 14.2	57.1 ± 15.3	62.2 ± 12.8
BMI (kg/m^2), mean ± SD	28.0 ± 6.7	28.4 ± 6.9	27.7 ± 6.5	26.9 ± 6.0	29.6 ± 7.2	26.9 ± 5.8	29.2 ± 7.9	26.2 ± 5.0
N with data	10491	4741	5750	2829	1313	954	479	89
<18.5 kg/m^2, n (%)	347 (3.3)	161 (3.4)	186 (3.2)	96 (3.4)	27 (2.1)	35 (3.7)	18 (3.8)	1 (1.1)
18.5–<25.0 kg/m^2, n (%)	3377 (32.2)	1451 (30.6)	1926 (33.5)	1066 (37.7)	314 (24.0)	339 (35.5)	142 (29.7)	37 (41.6)
25.0–<30.0 kg/m^2, n (%)	3444 (32.8)	1524 (32.1)	1920 (33.4)	963 (34.1)	424 (32.4)	336 (35.2)	133 (27.8)	35 (39.3)
≥30.0 kg/m^2, n (%)	3323 (31.7)	1605 (33.9)	1718 (29.9)	699 (24.8)	545 (41.6)	244 (25.6)	185 (38.7)	16 (18.0)

	Overall (N=11,243)	Primary care (N=5247)	All non-primary care[†] (N=5996)	University hospital (N=3005)	Research facility (N=1331)	Non-university hospital (N=979)	Specialists (N=493)	Private practice (N=90)
Smoking status, n (%)								
N with data	11201	5219	5982	3000	1324	978	492	90
Never smoked	4065 (36.3)	1981 (38.0)	2084 (34.8)	1091 (36.4)	410 (31.0)	332 (33.9)	166 (33.7)	24 (26.7)
Former smoker	5164 (46.1)	2312 (44.3)	2852 (47.7)	1480 (49.3)	628 (47.4)	507 (51.8)	169 (34.3)	44 (48.9)
Current smoker	1972 (17.6)	926 (17.7)	1046 (17.5)	429 (14.3)	286 (21.6)	139 (14.2)	157 (31.9)	22 (24.4)
Age at diagnosis, mean ± SD								
Asthma	35.2 ± 22.0	34.0 ± 22.3	36.2 ± 21.7	36.4 ± 21.3	34.0 ± 22.0	37.9 ± 21.6	44.8 ± 20.7	38.3 ± 20.6
COPD	58.4 ± 11.9	58.9 ± 11.6	57.9 ± 12.2	59.1 ± 11.2	57.2 ± 12.7	57.2 ± 12.4	55.9 ± 12.6	55.0 ± 16.8
Asthma or COPD	43.4 ± 22.1	42.8 ± 22.7	43.9 ± 21.6	44.1 ± 21.4	42.3 ± 22.2	45.3 ± 20.9	49.1 ± 18.5	45.5 ± 21.0
Time since diagnosis (years), mean ± SD								
Asthma	19.3 ± 18.2	20.0 ± 18.5	18.8 ± 17.9	17.5 ± 17.3	23.1 ± 19.2	18.9 ± 17.8	12.6 ± 15.6	19.6 ± 17.6
COPD	7.8 ± 8.9	7.6 ± 8.6	8.1 ± 9.2	7.6 ± 8.2	8.6 ± 9.3	9.2 ± 10.7	5.5 ± 8.3	10.3 ± 13.6
Asthma or COPD	15.4 ± 16.5	15.9 ± 16.8	15.0 ± 16.2	14.2 ± 15.6	17.9 ± 17.8	15.4 ± 16.2	9.5 ± 13.7	16.5 ± 16.7
Diagnosis of emphysema, n (%)	2120 (18.9)	888 (16.9)	1232 (20.5)	647 (21.5)	238 (17.9)	274 (28.0)	39 (7.9)	28 (31.1)
≥1 allergy reported, n (%)	5429 (48.3)	2536 (48.3)	2893 (48.2)	1388 (46.2)	687 (51.6)	450 (46.0)	270 (54.8)	40 (44.4)
Allergy testing performed, n (%)	2819 (25.1)	1131 (21.6)	1688 (28.2)	1022 (34.0)	235 (17.7)	243 (24.8)	148 (30.0)	18 (20.0)
Atopic, n (% of those with allergy testing)	2209 (78.4)	882 (78.0)	1327 (78.6)	756 (74.0)	207 (88.1)	187 (77.0)	143 (96.6)	17 (94.4)
Nasal or sinus polyps, n (%)	349 (3.1)	124 (2.4)	225 (3.8)	154 (5.1)	29 (2.2)	20 (2.0)	10 (2.0)	4 (4.4)
Patients with PRO data, n (%)	7791 (69.3)	3634 (69.3)	4157 (69.3)	2189 (72.8)	846 (63.6)	754 (77.0)	256 (51.9)	56 (62.2)
Asthma[§]	4115 (69.3)	1933 (68.7)	2182 (69.7)	1235 (73.1)	386 (62.2)	363 (76.7)	138 (58.7)	24 (60.0)
Asthma+COPD[§]	984 (70.5)	444 (69.3)	540 (71.5)	237 (75.0)	151 (66.5)	103 (76.3)	38 (70.4)	6 (46.2)
COPD[§]	2692 (68.9)	1257 (70.1)	1435 (67.9)	717 (71.7)	309 (64.0)	288 (77.6)	80 (39.2)	26 (70.3)

	Overall (N=11,243)	Primary care (N=5247)	All non-primary care[†] (N=5996)	University hospital (N=3005)	Research facility (N=1331)	Non-university hospital (N=979)	Specialists (N=493)	Private practice (N=90)
mMRC dyspnoea grade								
N with data	10 850	4970	5880	2984	1318	922	469	90
Grade ≥2, n (%)	3798 (35.0)	1655 (33.3)	2143 (36.4)	999 (33.5)	524 (39.8)	373 (40.5)	182 (38.8)	29 (32.2)
SGRQ total score, mean ± SD	35.1 ± 22.1	35.4 ± 22.0	35.0 ± 22.2	34.2 ± 22.3	36.1 ± 21.5	36.6 ± 22.5	32.5 ± 23.4	35.0 ± 19.9
CAAT total score, mean ± SD[**]	15.4 ± 8.6	15.7 ± 8.5	15.2 ± 8.6	14.6 ± 8.6	15.9 ± 8.3	16.1 ± 8.9	14.7 ± 8.8	14.3 ± 7.6
Patients with post-bronchodilator spirometry data, n (%)	9389 (83.5)	4217 (80.4)	5172 (86.3)	2656 (88.4)	1129 (84.8)	821 (83.9)	396 (80.3)	79 (87.8)
Asthma[§]	4917 (82.8)	2194 (78.0)	2723 (87.1)	1482 (87.7)	537 (86.5)	405 (85.6)	197 (83.8)	38 (95.0)
Asthma+COPD[§]	1188 (85.1)	537 (83.8)	651 (86.2)	288 (91.1)	192 (84.6)	107 (79.3)	47 (87.0)	8 (61.5)
COPD[§]	3284 (84.1)	1486 (82.9)	1798 (85.1)	886 (88.6)	400 (82.8)	309 (83.3)	152 (74.5)	33 (89.2)
Post-bronchodilator FEV_1 % predicted, mean ± SD[††]	75.4 ± 24.4	75.0 ± 24.4	75.7 ± 24.4	75.6 ± 24.4	76.8 ± 23.6	72.4 ± 26.3	78.9 ± 21.5	67.0 ± 21.6
Post-bronchodilator FEV_1/FVC, mean ± SD	0.66 ± 0.16	0.66 ± 0.16	0.66 ± 0.16	0.65 ± 0.16	0.68 ± 0.15	0.64 ± 0.18	0.74 ± 0.13	0.68 ± 0.14
Bronchodilator responsiveness (%), mean ± SD	6.7 ± 10.5	6.5 ± 10.3	6.8 ± 10.6	7.3 ± 9.9	5.7 ± 10.1	7.2 ± 11.3	5.8 ± 14.5	6.9 ± 8.1

Details of patients' care settings other than their recruitment sites are not available. For percentages, the denominator is given when different from the total number of patients (N with data [excluding 'unknown']). BMI: body mass index; CAAT: Chronic Airways Assessment Test; COPD: chronic obstructive pulmonary disease; eCRF: electronic case report form; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; mMRC: modified Medical Research Council; n: number of patients in the specified category; N: total number of patients; PRO: patient-reported outcome; SD: standard deviation; SGRQ: St George's Respiratory Questionnaire. [*]Approximately 80% of patients had post-bronchodilator spirometry data, 70% had PRO data and >90% had complete data for other variables. [†]Includes patients recruited from unknown care settings (N=98). [‡]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. Patients with COPD classified as 'very severe' were included in the 'severe' group. [§]Percentage values have been calculated as a proportion of total patients in that

physician-assigned diagnosis group, as opposed to the total patients from that respective care setting. [**]The CAAT is a trademark of the GlaxoSmithKline group of companies. 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. [††]Global Lung Function Initiative multi-ethnic reference equations were used to calculate % predicted values [3].

TABLE S4 Demographics, disease history and clinical characteristics of the NOVELTY population, by diagnosis or suspected diagnosis*

	Diagnosis (N=10,756)	**Suspected diagnosis (N=487)**
Physician-assigned diagnosis of asthma, n (%)†		
Mild	2079 (19.3)	96 (19.9)
Moderate	2086 (19.4)	22 (4.6)
Severe	1638 (15.2)	14 (2.9)
Physician-assigned diagnosis of asthma+COPD, n (%)†		
Mild	200 (1.9)	43 (8.9)
Moderate	536 (5.0)	90 (18.6)
Severe	452 (4.2)	71 (14.7)
Physician-assigned diagnosis of COPD, n (%)†		
Mild	1017 (9.5)	108 (22.4)
Moderate	1175 (10.9)	31 (6.4)
Severe	1566 (14.6)	8 (1.7)
Care setting		
Primary care	4960 (46.1)	287 (58.9)
Non-primary care‡	5796 (53.9)	200 (41.1)
Sex, n (%) female	5638 (52.4)	237 (48.7)
Age (years), mean ± SD	58.7 ± 15.8	58.7 ± 15.2
BMI (kg/m^2), mean ± SD	28.0 ± 6.7	29.5 ± 6.7
N with data	10 043	448
<18.5 kg/m^2, n (%)	339 (3.4)	8 (1.8)
18.5–<25.0 kg/m^2, n (%)	3274 (32.6)	103 (23.0)
25.0–<30.0 kg/m^2, n (%)	3299 (32.8)	145 (32.4)
≥30.0 kg/m^2, n (%)	3131 (31.2)	192 (42.9)
Smoking status, n (%)		
N with data	10 716	485
Never smoked	3948 (36.8)	117 (24.1)
Former smoker	4929 (46.0)	235 (48.5)
Current smoker	1839 (17.2)	133 (27.4)
Age at diagnosis, mean ± SD		
Asthma	34.7 ± 21.9	45.0 ± 22.1
COPD	58.5 ± 11.7	56.1 ± 14.3
Asthma or COPD	43.2 ± 22.1	47.6 ± 20.8
Diagnosis of emphysema, n (%)	2054 (19.1)	66 (13.6)
≥1 allergy reported, n (%)	5183 (48.2)	246 (50.5)
Allergy testing performed, n (%)	2722 (25.3)	97 (19.9)
Atopic, n (% of those with allergy testing)	2130 (78.3)	79 (81.4)
Nasal or sinus polyps, n (%)	335 (3.1)	14 (2.9)
mMRC dyspnoea grade		
N with data	10 375	475
Grade ≥2, n (%)	3652 (34.0)	146 (30.0)

SGRQ total score, mean ± SD	35.2 ± 22.2	34.9 ± 20.2
CAAT total score, mean ± SD[§]	15.5 ± 8.6	15.0 ± 8.0
Post-bronchodilator FEV_1 % predicted, mean ± SD[**]	75.2 ± 24.5	79.5 ± 22.2
Post-bronchodilator FEV_1/FVC, mean ± SD	0.66 ± 0.16	0.69 ± 0.14
Bronchodilator responsiveness (%), mean ± SD	6.7 ± 10.5	5.9 ± 10.8

For percentages, the denominator is given when different from the total number of patients (N with data [excluding 'unknown']). BMI: body mass index; CAAT: Chronic Airways Assessment Test; COPD: chronic obstructive pulmonary disease; eCRF: electronic case report form; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; mMRC: modified Medical Research Council; n: number of patients in the specified category; N: total number of patients; PRO: patient-reported outcome; SD: standard deviation; SGRQ: St George's Respiratory Questionnaire. [*]Approximately 80% of patients had post-bronchodilator spirometry data, 70% had PRO data and >90% had complete data for other variables. [†]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. Patients with COPD classified as 'very severe' were included in the 'severe' group. [‡]Includes patients recruited from university hospitals (N=3005), specialist research facilities (N=1331), non-university hospitals (N=979), specialist clinics (N=493), private practice (N=90), and unknown care settings (N=98). [§] 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. [**]Global Lung Function Initiative multi-ethnic reference equations were used to calculate % predicted values [3].

TABLE S5 Clinical characteristics of the NOVELTY population, by physician-assigned diagnosis

	Physician-assigned asthma (N=5940)*	**Physician-assigned asthma+COPD (N=1396)***	**Physician-assigned COPD (N=3907)***	**Total (N=11,243)***
Sex, n (%) female	3714 (62.5)	655 (46.9)	1506 (38.5)	5875 (52.3)
Age (years), mean ± SD	52.0 ± 17.1	64.7 ± 10.3	66.6 ± 9.6	58.7 ± 15.8
Ethnicity, n (%)				
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 (%)				
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, mean ± SD				
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, n (%)	1487 (25.0)	293 (21.0)	176 (4.5)	1956 (17.4)
Family history, n (%)				
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 (%)‡				
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)
Overall health status, n (% of patients with non-missing data)§				
N with non-missing data	4087	976	2688	7751
Very good	451 (11.0)	43 (4.4)	144 (5.4)	638 (8.2)
Good	1687 (41.3)	303 (31.0)	776 (28.9)	2766 (35.7)
Fair	1571 (38.4)	451 (46.2)	1297 (48.3)	3319 (42.8)
Poor	330 (8.1)	148 (15.2)	399 (14.8)	877 (11.3)
Very poor	48 (1.2)	31 (3.2)	72 (2.7)	151 (1.9)

	Physician-assigned asthma (N=5940)*	Physician-assigned asthma+COPD (N=1396)*	Physician-assigned COPD (N=3907)*	Total (N=11,243)*
mMRC dyspnoea grade				
N with data	5704	1343	3803	10 850
Grade ≥2, n (%)	1189 (20.8)	586 (43.6)	2023 (53.1)	3798 (35.0)
SGRQ total score, mean ± SD	29.9 ± 20.9	39.9 ± 22.1	41.5 ± 21.8	35.2 ± 22.1
CAAT total score, mean ± SD**	14.0 ± 8.5	17.2 ± 8.5	17.0 ± 8.3	15.4 ± 8.6
Exacerbations in the past 12 months, mean ± SD††	0.7 ± 1.5	1.0 ± 1.8	0.6 ± 1.3	0.7 ± 1.5
N with data	5892	1392	3870	11 154
≥1, n (%)	2008 (34.1)	654 (47.0)	1350 (34.9)	4012 (36.0)
≥2, n (%)	833 (14.1)	313 (22.5)	514 (13.3)	1660 (14.9)
Post-bronchodilator FEV_1 % predicted, mean ± SD‡‡	86.3 ± 20.3	68.3 ± 21.5	61.5 ± 23.0	75.4 ± 24.4
N with data (for LLN)	4799	1152	3198	9149
<LLN, n (%)	1363 (28.4)	706 (61.3)	2194 (68.6)	4263 (46.6)
Post-bronchodilator FEV_1/FVC, mean ± SD‡‡	0.74 ± 0.12	0.60 ± 0.15	0.57 ± 0.16	0.66 ± 0.16
N with data	4939	1187	3285	9411
<0.7, n (%)	1396 (28.3)	873 (73.5)	2463 (75.0)	4732 (50.3)
N with data (for LLN)	4819	1150	3202	9171
<LLN, n (%)	1118 (23.2)	711 (61.8)	2046 (63.9)	3875 (42.2)
FVC % predicted, mean ± SD				
Pre-bronchodilator	90.8 ± 17.7	85.1 ± 19.6	80.7 ± 20.9	86.5 ± 19.6
Post-bronchodilator	92.8 ± 17.1	88.9 ± 19.8	83.7 ± 20.5	89.1 ± 19.2
N with data	4766	1148	3195	9109
<LLN, n (%)	834 (17.5)	295 (25.7)	1064 (33.3)	2193 (24.1)
Bronchodilator responsiveness (%), mean ± SD	6.4 ± 9.5	8.1 ± 11.2	6.5 ± 11.5	6.7 ± 10.5
N with data	4777	1138	3119	9034
>12% and >200 mL, n (%)	759 (15.9)	217 (19.1)	409 (13.1)	1385 (15.3)
$FEF_{25–75}$ % predicted, mean ± SD				
Pre-bronchodilator	73.0 ± 38.0	48.6 ± 36.3	50.3 ± 37.5	62.7 ± 39.4
Post-bronchodilator	80.9 ± 39.2	52.7 ± 38.4	50.4 ± 37.1	67.3 ± 41.2
Inspiratory capacity (L), mean ± SD				
Pre-bronchodilator	2.6 ± 0.9	2.4 ± 0.8	2.2 ± 0.8	2.5 ± 0.8
Post-bronchodilator	2.8 ± 0.9	2.6 ± 0.9	2.3 ± 0.8	2.6 ± 0.9

	Physician-assigned asthma (N=5940)*	Physician-assigned asthma+COPD (N=1396)*	Physician-assigned COPD (N=3907)*	Total (N=11,243)*
Allergy testing performed, n (%)	2184 (36.8)	355 (25.4)	280 (7.2)	2819 (25.1)
Atopic, n (% of those with allergy testing)	1786 (81.8)	262 (73.8)	161 (57.5)	2209 (78.4)
Respiratory medications, n (%)§§				
N with medications data	5765	1373	3631	10 769
N with ICS dose data	5202	1373	3631	9876
No ICS***	627 (10.9)	218 (15.9)	1599 (44.0)	2444 (22.7)
Short-acting BD, no ICS***	488 (8.5)	148 (10.8)	839 (23.1)	1475 (13.7)
LABA and/or LAMA, no ICS***	49 (0.8)	137 (10.0)	1276 (35.1)	1462 (13.6)
Low-dose ICS	301 (5.8)	13 (1.0)	31 (0.9)	345 (3.5)
Low-dose ICS+LABA	960 (18.5)	110 (8.7)	174 (5.1)	1244 (12.6)
Med/high-dose ICS+LABA	1765 (33.9)	218 (17.3)	265 (7.8)	2248 (22.8)
ICS+LABA+LAMA†††	489 (8.5)	584 (42.5)	1252 (34.5)	2325 (21.6)
Maintenance OCS	340 (5.9)	83 (6.0)	97 (2.7)	520 (4.8)
Biologic therapy	566 (9.8)	58 (4.2)	3 (0.1)	627 (5.8)
Leukotriene modifier	1671 (29.0)	292 (21.3)	112 (3.1)	2075 (19.3)
Blood eosinophil count (10^9/μL), geo mean ± geo SD	0.17 ± 2.09	0.16 ± 2.02	0.15 ± 1.89	0.16 ± 2.01
N without OCS, anti-IL-4/4R or anti-IL-5/5R	2356	709	1716	4781
Excluding patients with OCS, anti-IL-4/4R or anti-IL-5/5R	0.17 ± 2.05	0.16 ± 2.01	0.15 ± 1.90	0.16 ± 2.00
Blood eosinophil proportion (% of total leukocytes), geo mean ± geo SD	2.30 ± 2.06	2.10 ± 2.03	1.76 ± 1.86	2.06 ± 2.00
Excluding patients with OCS, anti-IL-4/4R or anti-IL-5/5R	2.38 ± 2.00	2.15 ± 2.02	1.79 ± 1.86	2.12 ± 1.97
Blood neutrophil count (10^9/μL), geo mean ± geo SD	4.08 ± 1.46	4.44 ± 1.46	4.55 ± 1.43	4.31 ± 1.45
Blood neutrophil proportion (% of total leukocytes), geo mean ± geo SD	54.24 ± 1.18	58.29 ± 1.17	52.41 ± 1.17	54.14 ± 1.18

	Physician-assigned asthma (N=5940)*	Physician-assigned asthma+COPD (N=1396)*	Physician-assigned COPD (N=3907)*	Total (N=11,243)*
FeNO (ppb), median (IQR)				
Excluding current smokers	23 (14–40)	19 (12–32)	17 (11–27)	21 (13–35)
Current smokers	14 (8–26)	10 (6–18)	10 (6–17)	11 (7–19)

For percentages, the denominator is given when different from the total number of patients (N with data [excluding 'unknown']). BD: bronchodilator; CAAT: Chronic Airways Assessment Test; COPD: chronic obstructive pulmonary disease; eCRF: electronic case report form; $FEF_{25–75}$: forced expiratory flow at 25–75% of FVC; FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; geo: geometric; ICS: inhaled corticosteroid; IL-4/4R: interleukin-4 or interleukin-4 receptor; IL-5/5R: interleukin-5 or interleukin-5 receptor; IQR: interquartile range; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; LLN: lower limit of normal; med: medium; mMRC: modified Medical Research Council; n: number of patients in the specified category; N: total number of patients; OCS: oral corticosteroid; PRO: patient-reported outcome; SD: standard deviation; SGRQ: St George's Respiratory Questionnaire.
*Approximately 80% of patients had post-bronchodilator spirometry data, 70% had PRO data, 50% had biomarker data and >90% had complete data for other variables (see table 2 and table S2). †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 is the worse of the two physician-assigned severity classifications. Patients with COPD classified as 'very severe' were included in the 'severe' group. §From the question that precedes the SGRQ: "*please tick in one box to show how you describe your current health"*. **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. ††Among all patients, including those with no exacerbations. Includes mild, moderate and severe exacerbations, from the following question in the eCRF: *"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?"* ‡‡Global Lung Function Initiative multi-ethnic reference equations were used to calculate % predicted values [3]. §§Medication categories are defined in table S2. ICS dose was classified according to Global Initiative for Asthma 2019 definitions [2]. ***'No ICS' was defined as neither maintenance nor reliever ICS; †††Without maintenance OCS or biologic therapy.

TABLE S6 Demographics, disease history and clinical characteristics of the total NOVELTY population, by physician-assigned severity*

	Total		
	Mild (N=3543)*	**Moderate (N=3940)***	**Severe (N=3749)***
Physician-assigned diagnosis, n (%)†			
Asthma	2175 (61.4)	2108 (53.5)	1652 (44.1)
Asthma+COPD	243 (6.9)	626 (15.9)	523 (14.0)
COPD	1125 (31.8)	1206 (30.6)	1574 (42.0)
Sex, % female	1943 (54.8)	2071 (52.6)	1854 (49.5)
Age (years), mean ± SD	55.8 ± 16.9	59.3 ± 15.5	60.8 ± 14.5
BMI (kg/m^2), mean ± SD	27.9 ± 6.4	28.2 ± 6.9	27.9 ± 6.7
N with data	3349	3640	3496
<18.5 kg/m^2, n (%)	85 (2.5)	97 (2.7)	165 (4.7)
18.5–<25.0 kg/m^2, n (%)	1088 (32.5)	1188 (32.6)	1101 (31.5)
25.0–<30.0 kg/m^2, n (%)	1134 (33.9)	1177 (32.3)	1128 (32.3)
≥30.0 kg/m^2, n (%)	1042 (31.1)	1178 (32.4)	1102 (31.5)
Smoking status, n (%)			
N with data	3531	3927	3737
Never smoked	1469 (41.6)	1384 (35.2)	1211 (32.4)
Former smoker	1395 (39.5)	1826 (46.5)	1940 (51.9)
Current smoker	667 (18.9)	717 (18.3)	586 (15.7)
≥1 allergy reported, n (%)	1806 (51.0)	1932 (49.0)	1690 (45.1)
Allergy testing performed, n (%)	872 (24.6)	930 (23.6)	1015 (27.1)
Atopic, n (% of those with allergy testing)	693 (79.5)	701 (75.4)	815 (80.3)
Diagnosis of emphysema, n (%)	363 (10.2)	656 (16.6)	1099 (29.3)
Comorbidities, n (%)			
Chronic bronchitis	133 (3·8)	178 (4·5)	193 (5·1)
Bronchiectasis‡	109 (3·1)	191 (4·8)	308 (8·2)
Obstructive sleep apnoea	227 (6·4)	357 (9·1)	347 (9·3)
Allergic rhinitis	685 (19·3)	782 (19·8)	630 (16·8)
Recurrent/chronic non-allergic rhinitis/sinusitis	204 (5·8)	278 (7·1)	240 (6·4)
Nasal/sinus polyps	76 (2·1)	114 (2·9)	159 (4·2)
Hypertension	1039 (29·3)	1419 (36·0)	1318 (35·2)
Coronary artery disease or myocardial infarction	208 (5·9)	331 (8·4)	342 (9·1)
Congestive heart failure	34 (1·0)	67 (1·7)	108 (2·9)
Other cardiovascular disease§	253 (7·1)	339 (8·6)	362 (9·7)
Gastro-oesophageal reflux	504 (14·2)	639 (16·2)	591 (15·8)
Depression or anxiety	565 (15·9)	599 (15·2)	495 (13·2)
Type 2 diabetes	398 (11·2)	504 (12·8)	507 (13·5)
Osteoporosis	138 (3·9)	201 (5·1)	236 (6·3)
Chronic kidney disease	40 (1·1)	75 (1·9)	70 (1·9)
Inflammatory bowel disease	50 (1·4)	50 (1·3)	42 (1·1)

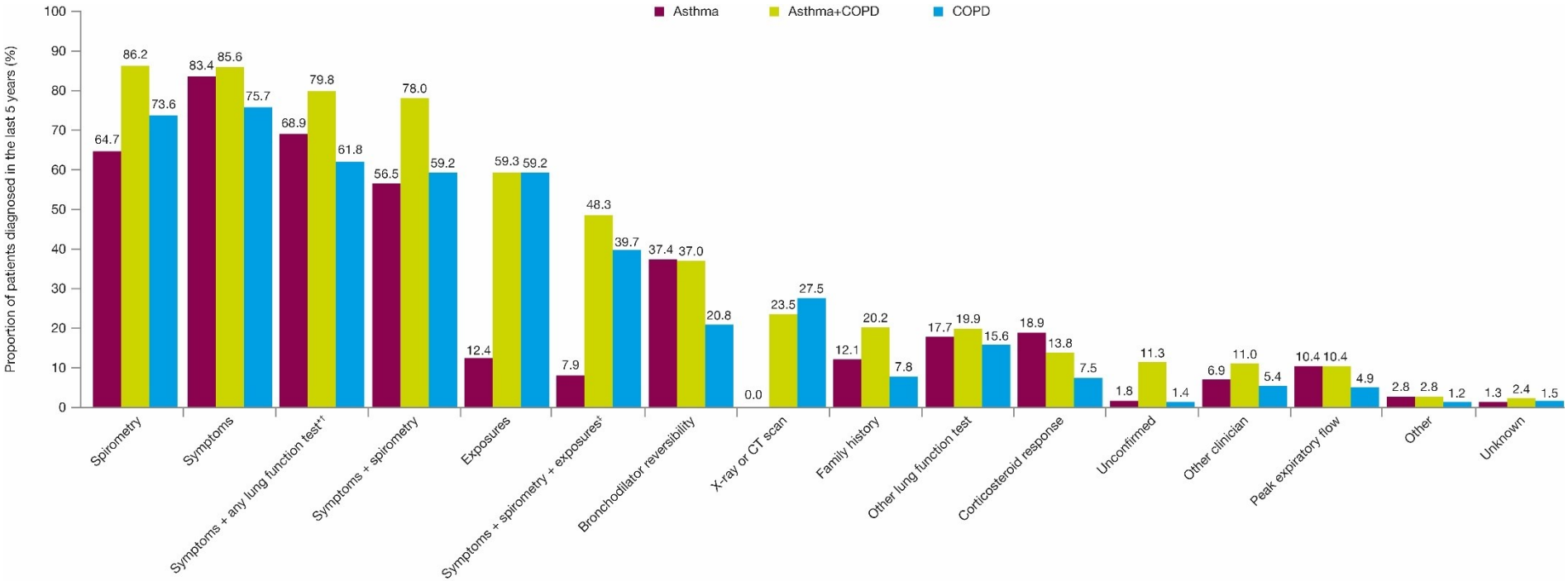
	Total		
	Mild (N=3543)*	**Moderate (N=3940)***	**Severe (N=3749)***
mMRC dyspnoea grade			
N with data	2370	2696	2679
Grade ≥2, n (%)	591 (16.7)	1102 (28.0)	2103 (56.1)
SGRQ total score, mean ± SD	26.3 ± 18.8	32.1 ± 20.8	46.1 ± 21.6
Overall health status, n (% of patients with non-missing data)**			
N with non-missing data	2370	2696	2679
Very good	306 (12.9)	226 (8.4)	106 (4.0)
Good	1010 (42.6)	1033 (38.3)	723 (27.0)
Fair	886 (37.4)	1121 (41.6)	1308 (48.8)
Poor	148 (6.2)	283 (10.5)	445 (16.6)
Very poor	20 (0.8)	33 (1.2)	97 (3.6)
CAAT total score, mean ± SD††	12.5 ± 7.7	14.4 ± 8.1	19.0 ± 8.5
Post-bronchodilator FEV_1 % predicted, mean ± SD‡‡	88.5 ± 17.9	78.4 ± 20.8	60.1 ± 24.9
Post-bronchodilator FEV_1/FVC, mean ± SD	0.74 ± 0.11	0.68 ± 0.14	0.57 ± 0.18
Bronchodilator responsiveness (%), mean ± SD	5.3 ± 9.0	6.1 ± 9.8	8.6 ± 12.0
N with data	2841	3116	3072
>12% and >200 mL, n (%)	352 (12.4)	457 (14.7)	576 (18.8)
Exacerbations in the past 12 months, mean ± SD§§	0.4 ± 1.0	0.6 ± 1.2	1.2 ± 1.9
N with data	3520	3906	3722
≥1, n (%)	838 (23.8)	1254 (32.1)	1916 (51.5)
≥2, n (%)	249 (7.1)	474 (12.1)	934 (25.1)
Healthcare utilisation, n (%)			
N with data	3520	3906	3722
≥1 hospital admission related to an exacerbation in the past 12 months	68 (1.9)	179 (4.6)	501 (13.5)
Respiratory medications, n (%)***			
N with medications data	3230	3845	3688
N with ICS dose data	2919	3527	3426
No ICS†††	998 (30.9)	819 (21.3)	627 (17.0)
Short-acting BD, no ICS†††	654 (20.2)	477 (12.4)	344 (9.3)
LABA and/or LAMA, no ICS†††	441 (13.7)	576 (15.0)	445 (12.1)
Low-dose ICS	255 (8.7)	72 (2.0)	18 (0.5)
Low-dose ICS+LABA	517 (17.7)	563 (16.0)	164 (4.8)
Med/high-dose ICS+LABA	586 (20.1)	1039 (29.5)	621 (18.1)
ICS+LABA+LAMA‡‡‡	257 (8.0)	770 (20.0)	1296 (35.1)
Maintenance OCS	56 (1.7)	119 (3.1)	345 (9.4)
Biologic therapy	16 (0.5)	69 (1.8)	542 (14.7)
Leukotriene modifier	464 (14.4)	762 (19.8)	848 (23.0)

	Total		
	Mild (N=3543)*	**Moderate (N=3940)***	**Severe (N=3749)***
Blood eosinophil count (10^9/μL), geo mean ± geo SD	0.15 ± 1.95	0.16 ± 2.02	0.16 ± 2.06
N without OCS/anti-IL-5/5R	1514	1679	1587
Excluding patients with OCS/anti-IL-5/5R	0.15 ± 1.96	0.16 ± 2.01	0.17 ± 2.02
Blood eosinophil proportion (% of total leukocytes), geo mean ± geo SD	2.12 ± 1.92	2.19 ± 1.99	1.89 ± 2.08
Excluding patients with OCS, anti-IL-4/4R or anti-IL-5/5R	2.17 ± 1.92	2.21 ± 1.98	1.97 ± 2.02
Blood neutrophil count (10^9/μL), geo mean ± geo SD	4.01 ± 1.42	4.23 ± 1.44	4.69 ± 1.47
Blood neutrophil proportion (% of total leukocytes), geo mean ± geo SD	54.24 ± 1.18	55.68 ± 1.17	52.61 ± 1.17
FeNO (ppb), median (IQR)			
Excluding current smokers	21 (13–35)	21 (13–36)	20 (12–34)
Current smokers	12 (7–21)	10 (6–17.75)	10 (6–18)

For percentages, the denominator is given when different from the total number of patients (N with data [excluding 'unknown']). BD: bronchodilator; BMI: body mass index; CAAT: Chronic Airways Assessment Test; COPD: chronic obstructive pulmonary disease; eCRF: electronic case report form; FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; geo: geometric; ICS: inhaled corticosteroid; IL-5/5R: interleukin-5 or interleukin-5 receptor; IQR: interquartile range; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; Med: medium; mMRC: modified Medical Research Council; n: number of patients in the specified category; N: total number of patients; OCS: oral corticosteroid; PRO: patient-reported outcome; SD: standard deviation; SGRQ: St George's Respiratory Questionnaire. *Approximately 80% of patients had post-bronchodilator spirometry data, 70% had PRO data, 50% had biomarker data and >90% had complete data for other variables. †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. Patients with COPD classified as 'very severe' were included in the 'severe' group. ‡From an eCRF entry under 'Respiratory Comorbidities' and/or from a record of abnormal CT findings. §Any cardiovascular disease other than hypertension, coronary artery disease, myocardial infarction, or congestive heart failure. **From the question that precedes the SGRQ: "*please tick in one box to show how you describe your current health*". ††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. ‡‡Global Lung Function Initiative multi-ethnic reference equations were used to calculate % predicted values [3]. §§Among all patients, including those with no exacerbations. Exacerbations include mild, moderate and severe exacerbations, from the following question in the eCRF: "*During the past 12 months, on how many occasions has your patient experienced an exacerbation of*

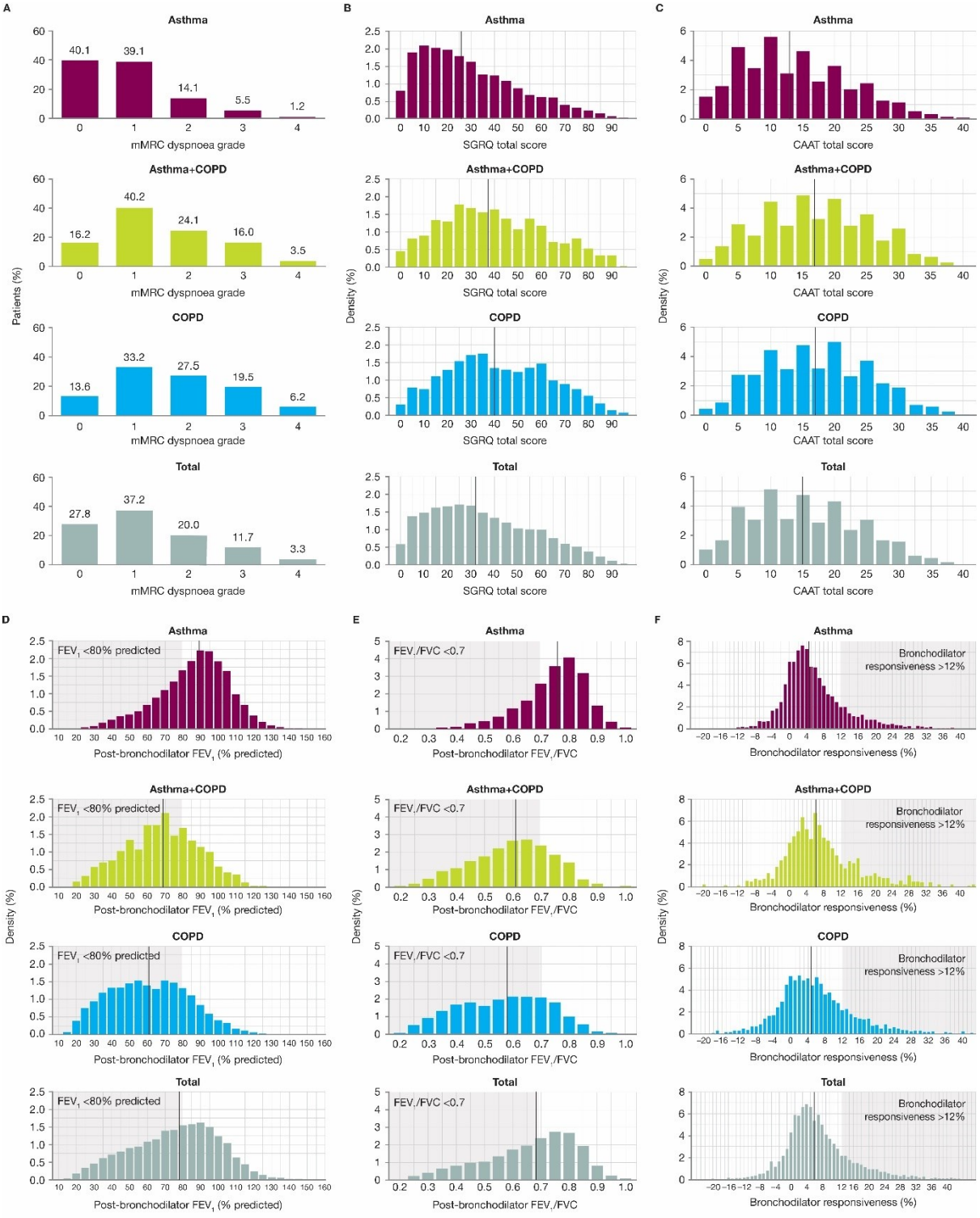
their asthma or COPD beyond the patient's usual day to day variance?" [***]Medication categories are defined in table S2. ICS dose was classified according to Global Initiative for Asthma 2019 definitions [2]. [†††]'No ICS' was defined as neither maintenance nor reliever ICS; [‡‡‡]Without maintenance OCS or biologic therapy.

FIGURE S1 Criteria that physicians reported having used in making a diagnosis of asthma and/or COPD among patients diagnosed in the last 5 years.



Criteria were selected from a checklist including all of the listed items; multiple criteria could be selected. COPD=chronic obstructive pulmonary disease. CT: computed tomography. *Any lung function test includes spirometry, bronchodilator reversibility, peak expiratory flow or other lung function test. †Consistent with the recommendations of the Global Initiative for Asthma for initial diagnosis of asthma (before treatment) [2]. ‡Consistent with the criteria required by the Global Initiative for Chronic Obstructive Lung Disease for diagnosis of COPD [4].

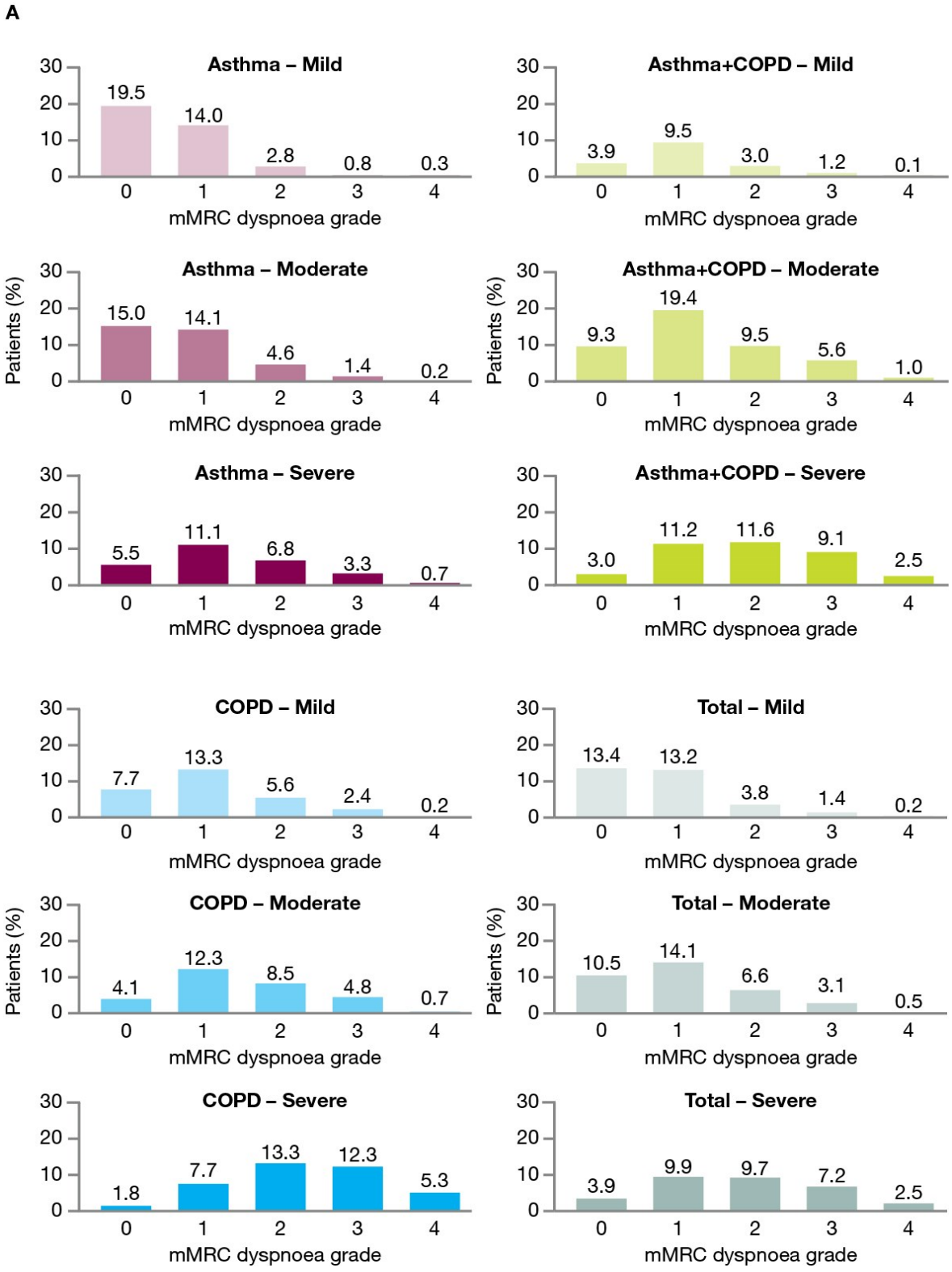
FIGURE S2 Distribution of patient-reported symptoms and health status (A, B,* C), and spirometry data (D,† E, F) by physician-assigned diagnosis group and among all NOVELTY patients.

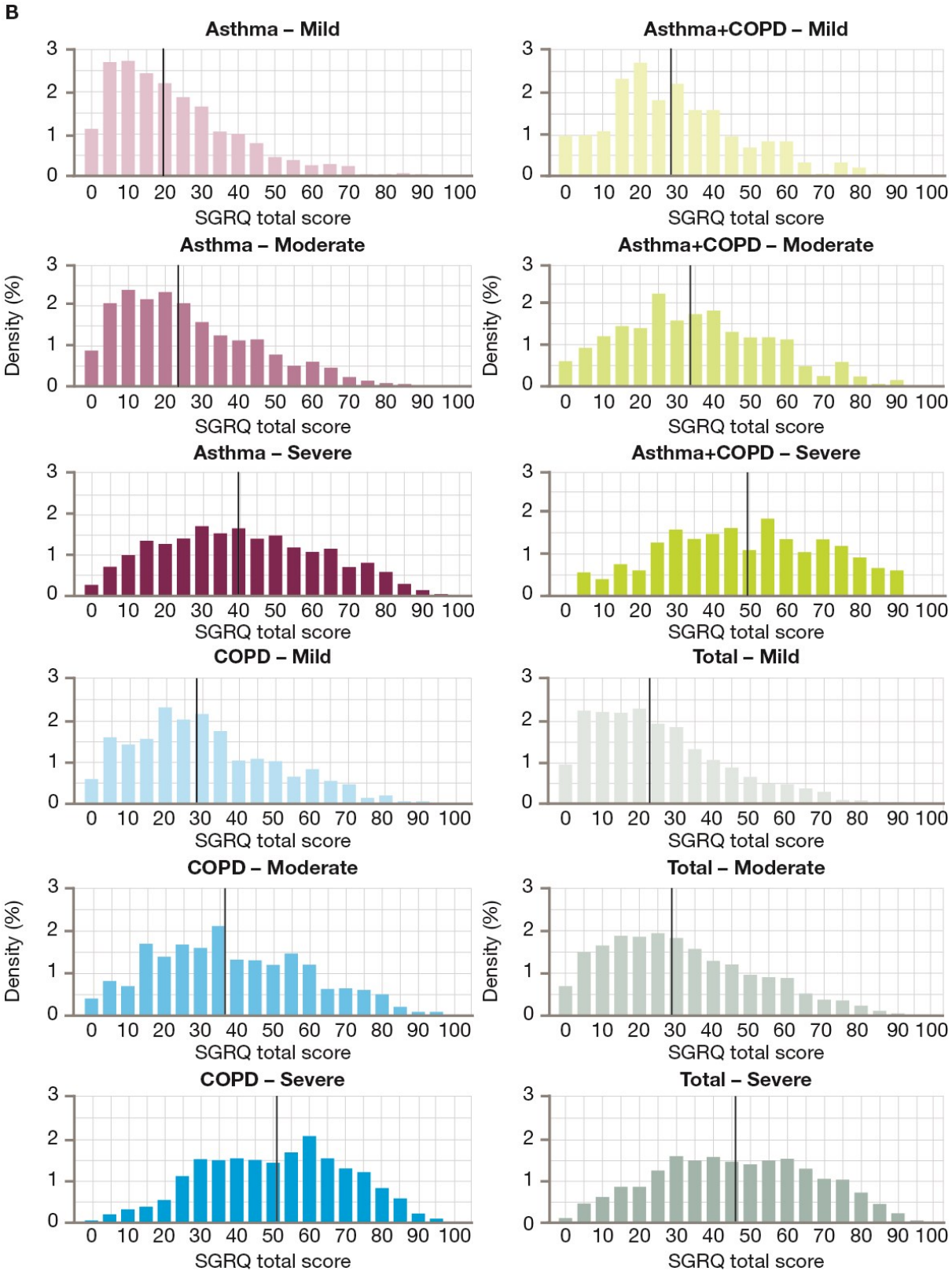


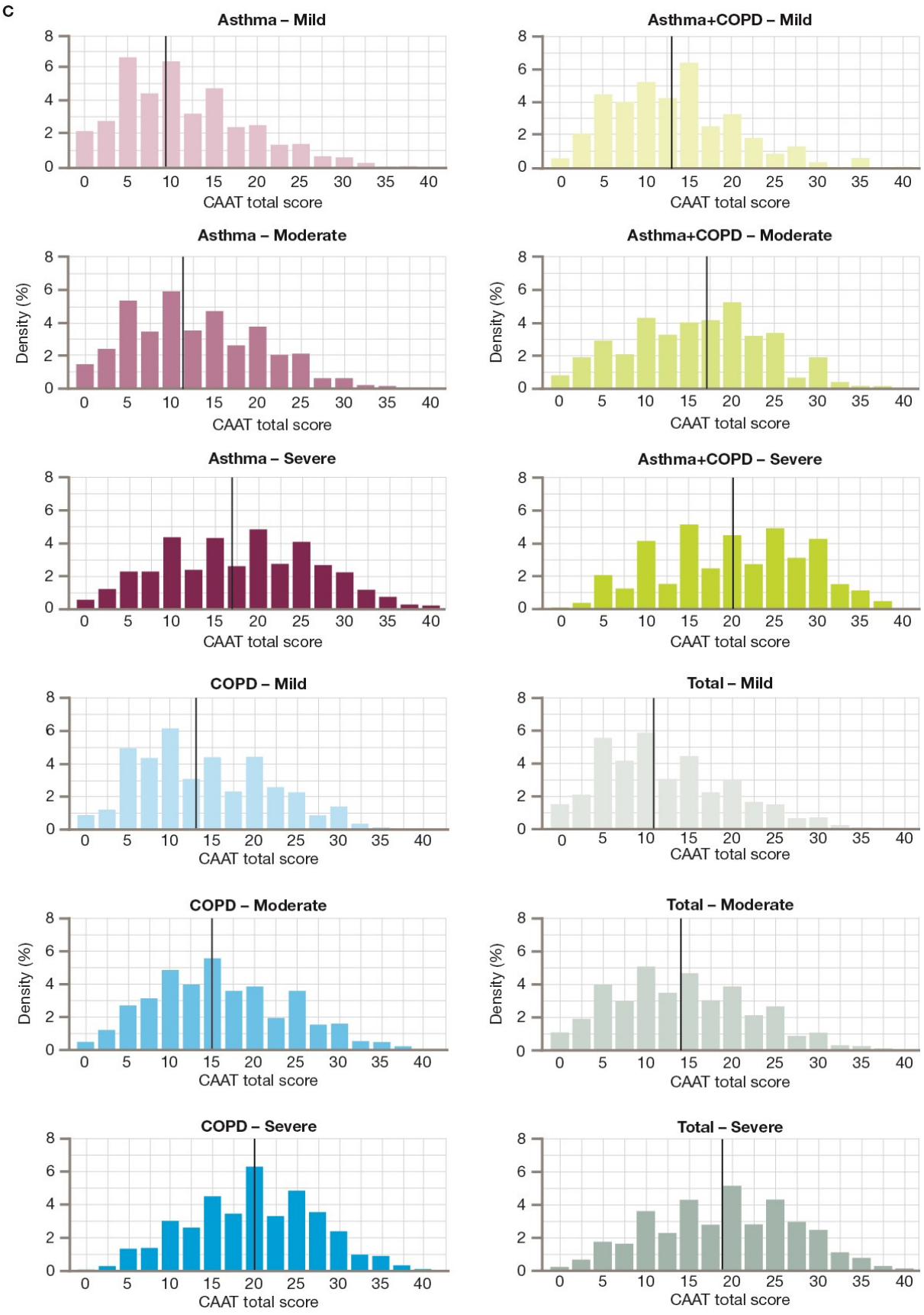
For continuous data, density is calculated as frequency divided by category width. The solid

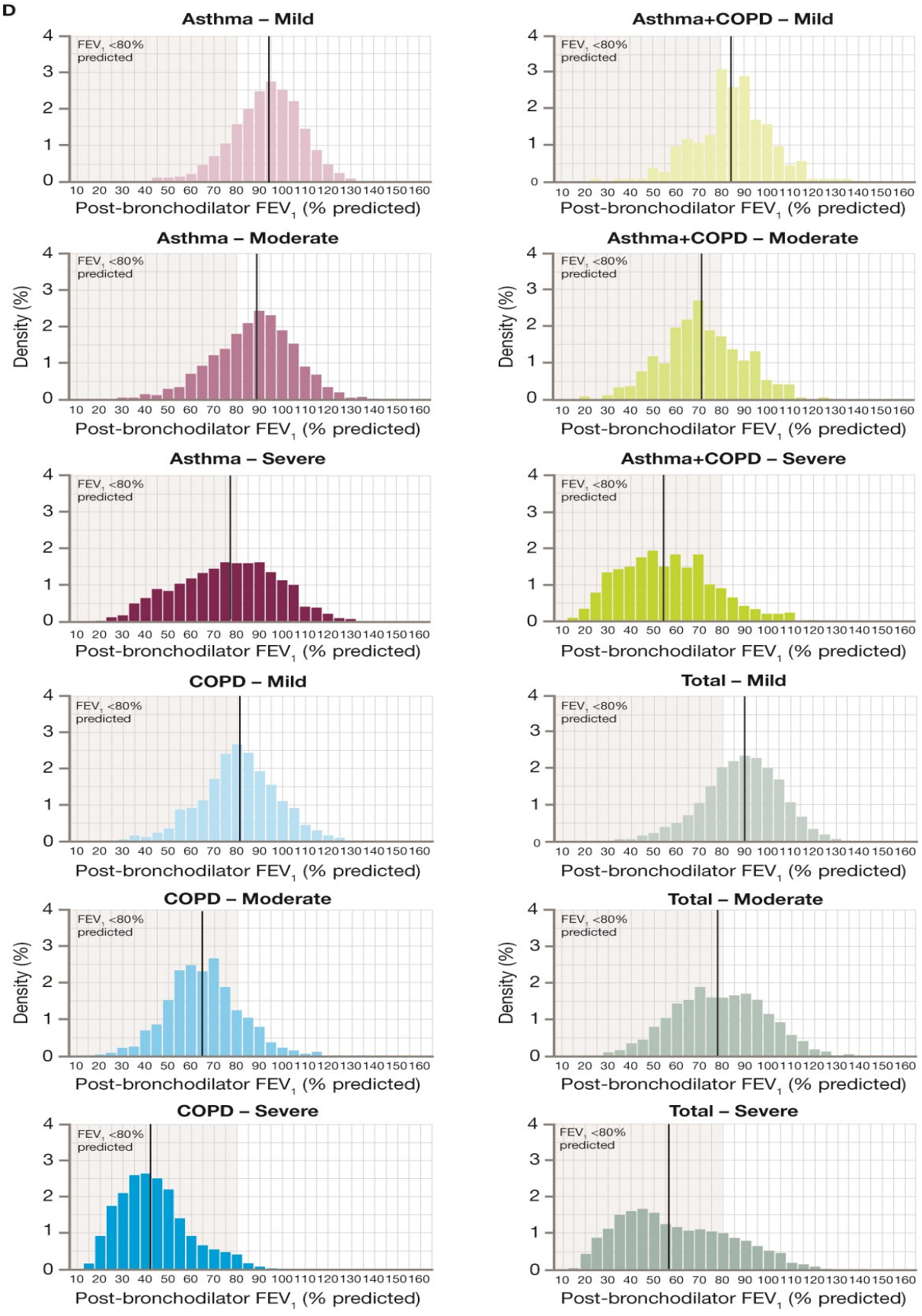
black lines show median values. Grey shading shows spirometric thresholds used in asthma/COPD diagnostic criteria [4, 5]. See table 2 and table S2 for the number of patients with spirometry and PRO data. CAAT: Chronic Airways Assessment Test; COPD; chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; mMRC: modified Medical Research Council; PRO: patient-reported outcome; SGRQ: St George's Respiratory Questionnaire. *The CAAT is a trademark of the GlaxoSmithKline group of companies. 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. †Global Lung Function Initiative multi-ethnic reference equations were used to calculate % predicted values [3].

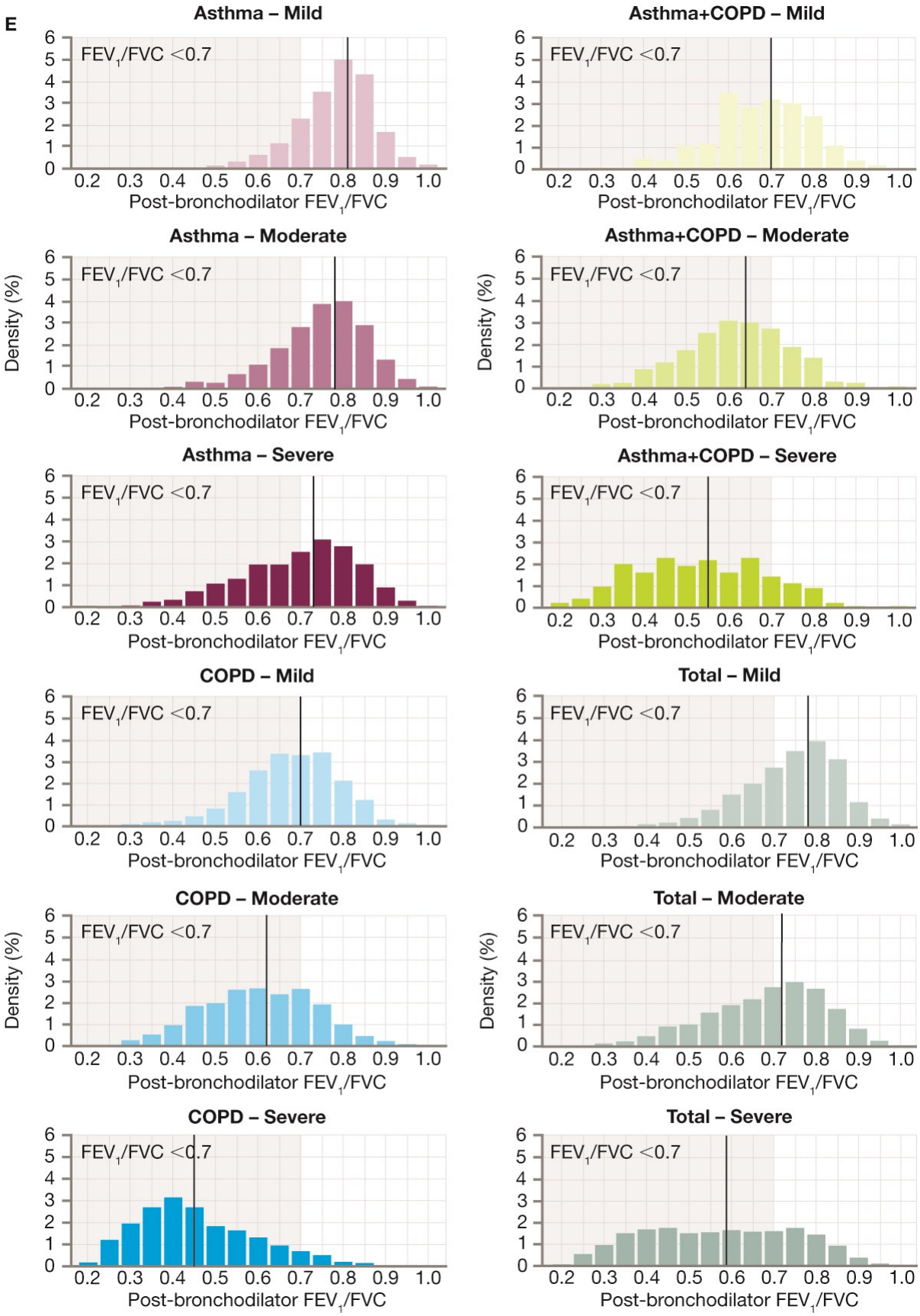
FIGURE S3 Heterogeneity in patient-reported symptoms and health status (A, B, C) and spirometry data (D, E, F) by physician-assigned diagnosis and/or severity.

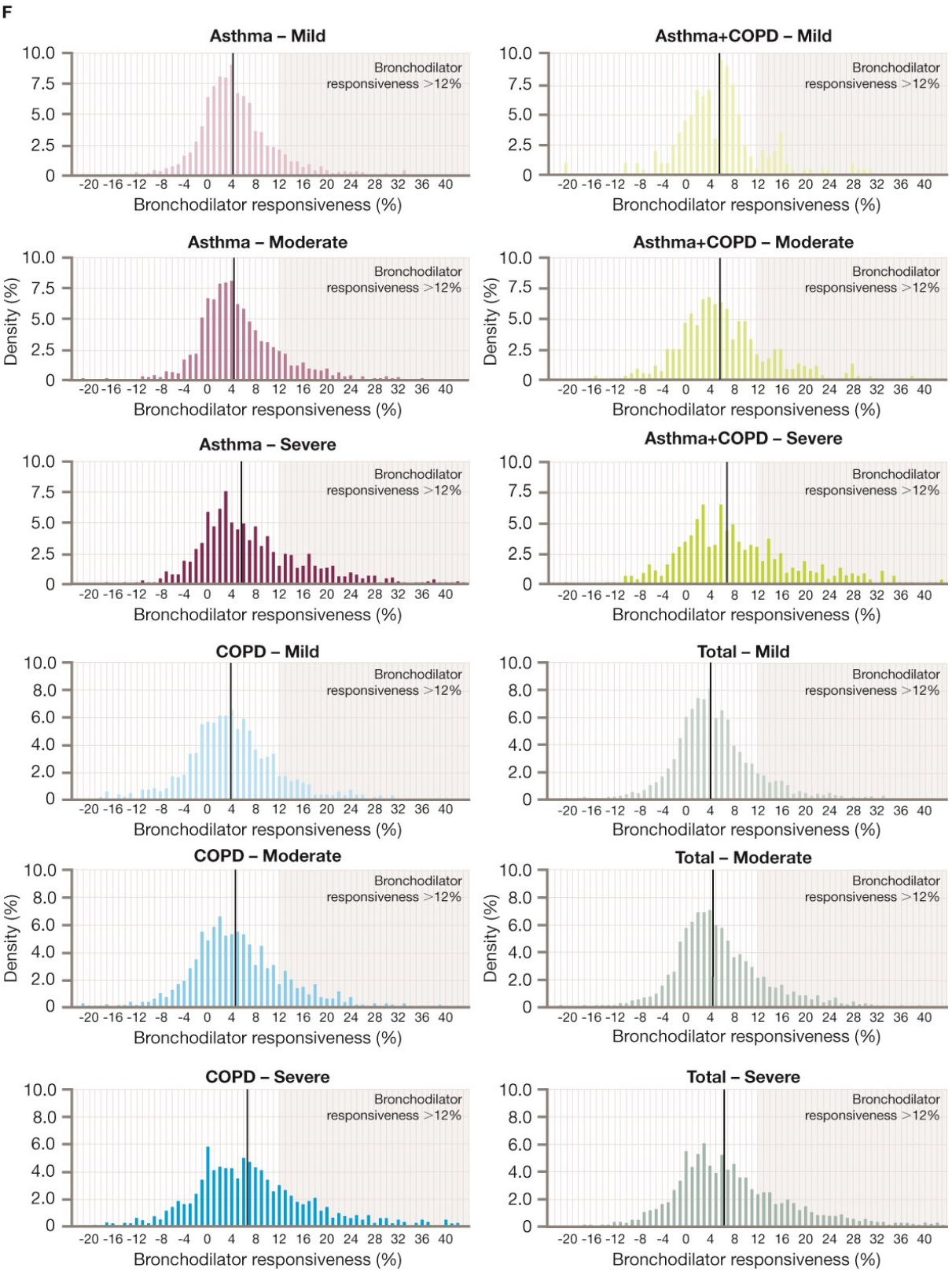



B
Asthma – Mild
Asthma+COPD – Mild
Asthma – Moderate
Asthma+COPD – Moderate
Asthma – Severe
Asthma+COPD – Severe
COPD – Mild
Total – Mild
COPD – Moderate
Total – Moderate
COPD – Severe
Total – Severe
Density (%)
SGRQ total score
0 10 20 30 40 50 60 70 80 90 100
0 1 2 3


C
Asthma – Mild
Asthma+COPD – Mild
Asthma – Moderate
Asthma+COPD – Moderate
Asthma – Severe
Asthma+COPD – Severe
COPD – Mild
Total – Mild
COPD – Moderate
Total – Moderate
COPD – Severe
Total – Severe
Density (%)
CAAT total score
0 5 10 15 20 25 30 35 40
0 2 4 6 8


D
Asthma – Mild
Asthma+COPD – Mild
Asthma – Moderate
Asthma+COPD – Moderate
Asthma – Severe
Asthma+COPD – Severe
COPD – Mild
Total – Mild
COPD – Moderate
Total – Moderate
COPD – Severe
Total – Severe
FEV1 <80% predicted
Density (%)
Post-bronchodilator FEV1 (% predicted)
0 1 2 3 4
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160

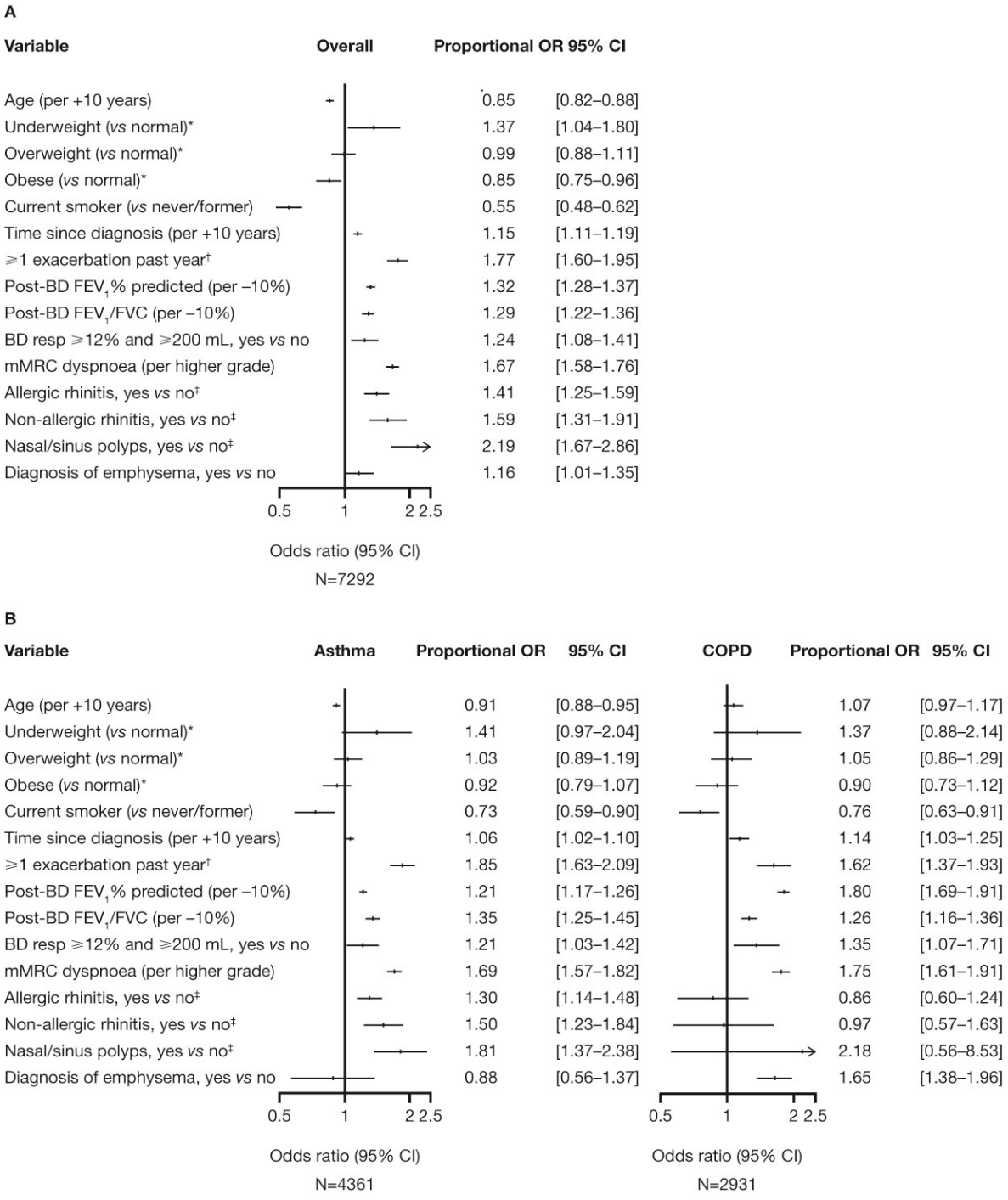

E
Asthma – Mild
Asthma+COPD – Mild
Asthma – Moderate
Asthma+COPD – Moderate
Asthma – Severe
Asthma+COPD – Severe
COPD – Mild
Total – Mild
COPD – Moderate
Total – Moderate
COPD – Severe
Total – Severe
FEV1/FVC <0.7
Density (%)
Post-bronchodilator FEV1/FVC
0 1 2 3 4 5 6
0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0



For continuous data, density is calculated as frequency divided by category width. The solid black lines show median values. Grey shading shows spirometric thresholds used in asthma/COPD diagnostic criteria [4, 5]. See table 2 and table S2 for the number of patients with spirometry and PRO data. CAAT: Chronic Airways Assessment Test; COPD: chronic

obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; mMRC: modified Medical Research Council; SGRQ: St George's Respiratory Questionnaire. *The CAAT is a trademark of the GlaxoSmithKline group of companies. 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. †Global Lung Function Initiative multi-ethnic reference equations were used to calculate % predicted values [3].

FIGURE S4 Proportional odds ratios from multivariable ordinal regression models for factors associated with physician-assigned severity in patients with asthma or COPD overall (A) and for asthma and COPD separately (B)



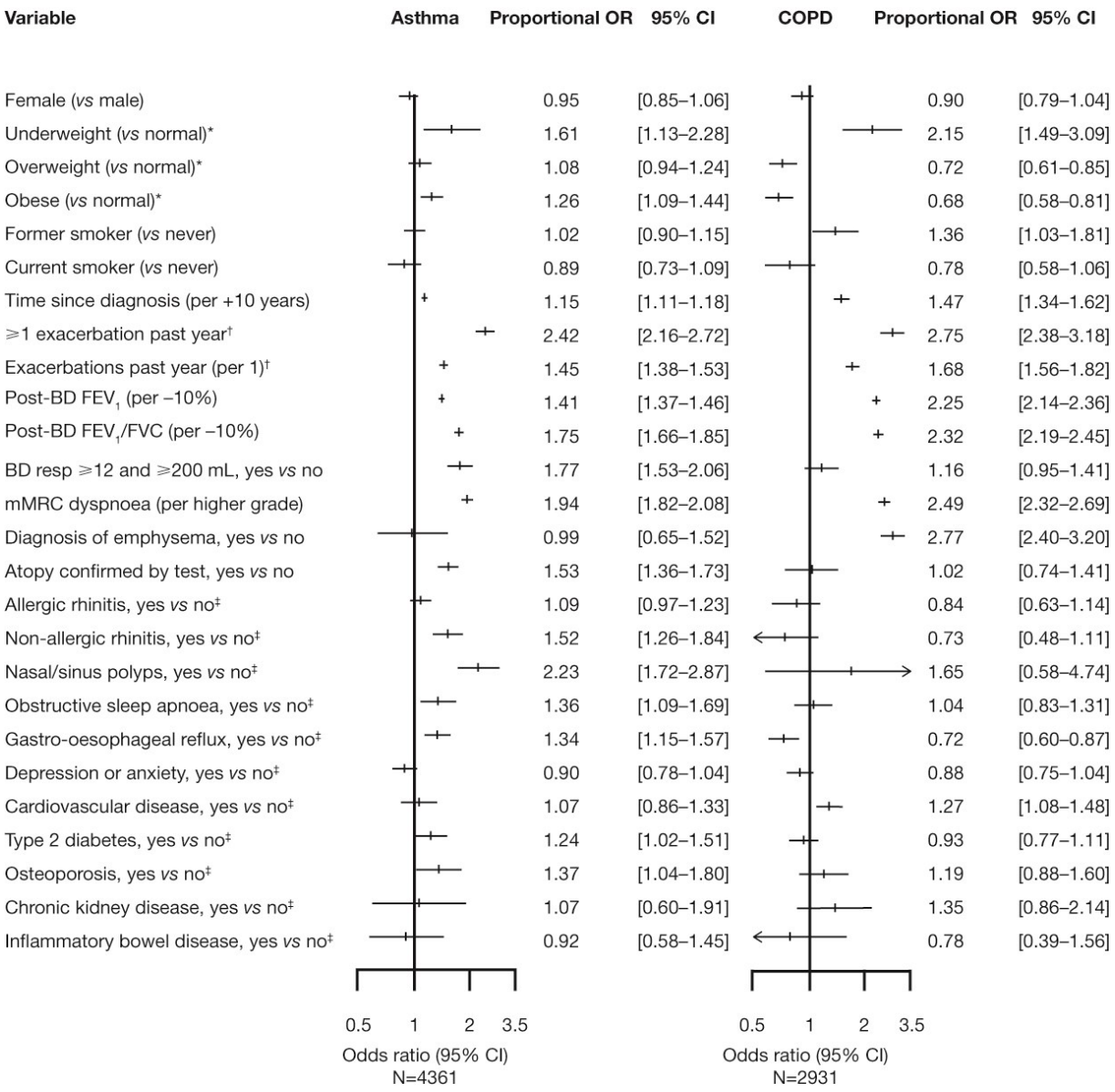
Proportional odds ratios represent the odds of having higher physician-assigned severity (severe *vs* mild or moderate, moderate *vs* mild) per the increment stated for continuous variables, or for different levels of categorical variables (*vs* their reference). See supplementary material page 2 for details of the methodology. Patients with asthma+COPD were excluded because, for them, the severity category was assigned as the higher of the

physician's two severity classifications for asthma and for COPD. Only patients without missing data for the selected variables were included. Univariate associations are shown in figure S5. *Body mass index categories (kg/m^2): underweight: <18.5, normal: 18.5 to <25, overweight: 25 to <30, obese; ≥30. †Exacerbations include mild, moderate and severe exacerbations, from the following question in the eCRF: *"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?"* ‡Comorbidities were recorded by the physician *via* a checklist; therefore, the 'no' group includes both 'not present' and 'unknown'. BD: bronchodilator; CI: confidence interval; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; mMRC: modified Medical Research Council; N: total number of patients; OR: odds ratio; Resp: responsiveness.

Summary of findings for panel A: Multivariable ordinal regression analysis among all patients with asthma or COPD showed that several clinical and spirometric factors were associated with greater physician-assessed severity. Notably, current smoking was associated with *lower* severity classification than never/former smoking; obesity was also independently associated with lower severity.

Summary of findings for panel B: Multivariable ordinal regression analyses for asthma and COPD separately showed that higher mMRC dyspnoea grade, longer time since diagnosis, ≥1 exacerbation in the previous year, bronchodilator responsiveness and lower post-bronchodilator FEV_1/FVC were associated with greater severity in both asthma and COPD. Younger age, allergic and non-allergic rhinitis and nasal or sinus polyps were associated with greater severity of asthma, together with allergic and non-allergic rhinitis and nasal or sinus polyps, whereas a diagnosis of emphysema was associated with greater severity of COPD, independent of lung function. The post-bronchodilator FEV_1 % predicted was more strongly associated with severity in COPD than in asthma.

FIGURE S5 Proportional odds ratios from univariate ordinal regression models for factors associated with physician-assigned severity in patients with physician-assigned diagnoses of asthma or COPD



Proportional odds ratios represent the odds of having higher physician-assigned severity (severe *vs* mild or moderate, moderate *vs* mild) per the increment stated for continuous variables, or for different levels of categorical variables (*vs* their reference). See supplementary material page 2 for details of methodology. Patients with asthma+COPD were excluded because for them, the severity category was assigned as the higher of the physician's two severity classifications for asthma and for COPD. Only patients without missing data for the selected variables were included. *Body mass index categories (kg/m^2): underweight: <18.5, normal: 18.5 to <25, overweight: 25 to <30, obese; ≥30. †Exacerbations include mild, moderate and severe exacerbations, from the following question in the eCRF: *"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?"*

‡Comorbidities were recorded by the physician via a checklist; therefore, the 'no' group includes both 'not present' and 'unknown'. BD: bronchodilator; CI: confidence interval; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; mMRC: modified Medical Research Council; N: total number of patients; OR: odds ratio; Resp: responsiveness.

TABLE S7 List of NOVELTY study investigators

Investigator	Country	Investigator	Country
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Gustavo Marino	Argentina	Keita Hosoi	Japan
Walter Mattarucco	Argentina	Yumiko Ide	Japan
Juan Nogueira	Argentina	Minehiko Inomata	Japan
Maria Parody	Argentina	Hiromasa Inoue	Japan
Pablo Pascale	Argentina	Koji Inoue	Japan
Pablo Rodriguez	Argentina	Sumito Inoue	Japan
Damian Silva	Argentina	Motokazu Kato	Japan
Graciela Svetliza	Argentina	Masayuki Kawasaki	Japan
Carlos F. Victorio	Argentina	Tomotaka Kawayama	Japan
Roxana Willigs Rolon	Argentina	Toshiyuki Kita	Japan
Anahi Yañez	Argentina	Kanako Kobayashi	Japan
Stuart Baines	Australia	Hiroshi Koto	Japan
Simon Bowler	Australia	Koichi Nishi	Japan
Peter Bremner	Australia	Junpei Saito	Japan
Sheetal Bull	Australia	Yasuo Shimizu	Japan
Patrick Carroll	Australia	Toshihiro Shirai	Japan
Mariam Chaalan	Australia	Naruhiko Sugihara	Japan
Claude Farah	Australia	Ken-ichi Takahashi	Japan
Gary Hammerschlag	Australia	Hiroyuki Tashimo	Japan
Kerry Hancock	Australia	Keisuke Tomii	Japan
Zinta Harrington	Australia	Takashi Yamada	Japan
Gregory Katsoulotos	Australia	Masaru Yanai	Japan
Joshua Kim	Australia	Ruth Cerino Javier	Mexico
David Langton	Australia	Alfredo Domínguez Peregrina	Mexico
Donald Lee	Australia	Marco Fernández Corzo	Mexico
Matthew Peters	Australia	Efraín Montano Gonzalez	Mexico
Lakshman Prassad	Australia	Alejandra Ramírez-Venegas	Mexico
Helen Reddel	Australia	Adrian Rendon	Mexico
Dimitar Sajkov	Australia	Willem Boersma	Netherlands
Francis Santiago	Australia	R.S. Djamin	Netherlands
Frederick Graham Simpson	Australia	Michiel Eijsvogel	Netherlands
Sze Tai	Australia	Frits Franssen	Netherlands
Paul Thomas	Australia	Martijn Goosens	Netherlands
Peter Wark	Australia	Lidwien Graat-Verboom	Netherlands
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Thúlio Cunha	Brazil	Rob Janssen	Netherlands
Marina Lima	Brazil	Kim Kuppens	Netherlands
Alexandre Pinto Cardoso	Brazil	Maarten van den Berge	Netherlands
Marcelo Rabahi	Brazil	Mario van de Ven	Netherlands
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Amarjit Cheema	Canada
Guy Chouinard	Canada
Michael Csanadi	Canada
Anil Dhar	Canada
Ripple Dhillon	Canada
J. Mark FitzGerald	Canada
David Kanawaty	Canada
Allan Kelly	Canada
William Killorn	Canada
Daniel Landry	Canada
Robert Luton	Canada
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Andrew McIvor	Canada
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Kim Ming Christopher Hui	China[a]
Manxiang Li	China[a]
Shiyue Li	China[a]
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Yijun Tang	China[a]
Chen Wang	China[a]
Tan Wang	China[a]
Fuqiang Wen	China[a]
Feng Wu	China[a]
PingChao Xiang	China[a]
Zuke Xiao	China[a]
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Jinghua Yang	China[a]
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Caiqing Zhang	China[a]
Min Zhang	China[a]
Ping Zhang	China[a]
Wei Zhang	China[a]
Xiaohe Zheng	China[a]
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Alejandra Cañas Arboleda	Colombia
Carlos Matiz Bueno	Colombia
Dora Molina de Salazar	Colombia
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Alamdar Khusrawi	Norway
Torbjorn Oien	Norway
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Young Joo Cho	South Korea
Yong Il Hwang	South Korea
Woo Jin Kim	South Korea
Young-Il Koh	South Korea
Byung-Jae Lee	South Korea
Kwan-Ho Lee	South Korea
Sang-Pyo Lee	South Korea
Yong Chul Lee	South Korea
Seong Yong Lim	South Korea
Kyung Hun Min	South Korea
Yeon-Mok Oh	South Korea
Choon-Sik Park	South Korea
Hae-Sim Park	South Korea
Heung-Woo Park	South Korea
Chin Kook Rhee	South Korea
Ho Joo Yoon	South Korea
Hyoung-Kyu Yoon	South Korea
Alvar Agusti García-Navarro	Spain
Rubén Andújar	Spain
Laura Anoro	Spain
María Buendía García	Spain
Paloma Campo Mozo	Spain
Sergio Campos	Spain
Francisco Casas Maldonado	Spain
Manuel Castilla Martínez	Spain
Carolina Cisneros Serrano	Spain
Lorena Comeche Casanova	Spain
Dolores Corbacho	Spain
Felix Del Campo Matías	Spain
Jose Echave-Sustaeta	Spain
Gloria Francisco Corral	Spain
Pedro Gamboa Setién	Spain
Marta García Clemente	Spain
Ignacio García Núñez	Spain
Jose García Robaina	Spain
Mercedes García Salmones	Spain
Jose Maria Marín Trigo	Spain
Marta Nuñez Fernandez	Spain
Sara Nuñez Palomo	Spain
José Olaguibel Rivera	Spain
Luis Pérez de Llano	Spain
Ana Pueyo Bastida	Spain
Ana Rañó	Spain
José Rodríguez González-	Spain

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Carsten Kjellerup	Denmark	José Velasco Garrido	Spain
Ulla Weinreich	Denmark	Dan Curiac	Sweden
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Olivier Brun	France	Cornelia Lif-Tiberg	Sweden
Pierre-Régis Burgel	France	Anders Luts	Sweden
Christos Chouaid	France	Lennart Råhlen	Sweden
Francis Couturaud	France	Stefan Rustscheff	Sweden
Jacques de Blic	France	Frances Adams	UK
Didier Debieuvre	France	Drew Bradman	UK
Dominique Delsart	France	Emma Broughton	UK
Axelle Demaegdt	France	John Cosgrove	UK
Pascal Demoly	France	Patrick Flood-Page	UK
Antoine Deschildre	France	Liz Fuller	UK
Gilles Devouassoux	France	Timothy Harrison	UK
Carole Egron	France	David Hartley	UK
Lionel Falchero	France	Keith Hattotuwa	UK
François Goupil	France	Gareth Jones	UK
Romain Kessler	France	Keir Lewis	UK
Pascal Le Roux	France	Lorcan McGarvey	UK
Pascal Mabire	France	Alyn Morice	UK
Guillaume Mahay	France	Preeti Pandya	UK
Stéphanie Martinez	France	Manish Patel	UK
Boris Melloni	France	Kay Roy	UK
Laurent Moreau	France	Ramamurthy Sathyamurthy	UK
Chantal Raherison	France	Swaminathan Thiagarajan	UK
Emilie Riviere	France	Alice Turner	UK
Pauline Roux-Claudé	France	Jorgen Vestbo	UK
Michel Soulier	France	Wisia Wedzicha	UK
Guillaume Vignal	France	Tom Wilkinson	UK
Azzedine Yaici	France	Pete Wilson	UK
Sven Philip Aries	Germany	Lo'Ay Al-Asadi	USA
Robert Bals	Germany	James Anholm	USA
Ekkehard Beck	Germany	Frank Averill	USA
Andreas Deimling	Germany	Sandeep Bansal	USA
Jan Feimer	Germany	Alan Baptist	USA
Vera Grimm-Sachs	Germany	Colin Campbell	USA
Gesine Groth	Germany	Michael A. Campos	USA
Felix Herth	Germany	Bradley Chipps	USA
Gerhard Hoheisel	Germany	Gretchen Crook	USA
Frank Kanniess	Germany	Samuel DeLeon	USA
Thomas Lienert	Germany	Alain Eid	USA
Silke Mronga	Germany	Ellen Epstein	USA
Jörg Reinhardt	Germany	Stephen Fritz	USA
Christian Schlenska	Germany	Hoadley Harris	USA
Christoph Stolpe	Germany	Mitzie Hewitt	USA
Ishak Teber	Germany	Fernando Holguin	USA

Hartmut Timmermann	Germany	Golda Hudes	USA
Thomas Ulrich	Germany	Richard Jackson	USA
Peter Velling	Germany	Alan Kaufman	USA
Sabina Wehgartner-Winkler	Germany	David Kaufman	USA
Juergen Welling	Germany	Ari Klapholz	USA
Ernst-Joachim Winkelmann	Germany	Harshavardhan Krishna	USA
Carlo Barbetta	Italy	Daria Lee	USA
Fulvio Braido	Italy	Robert Lin	USA
Vittorio Cardaci	Italy	Diego Maselli-Caceres	USA
Enrico Maria Clini	Italy	Vinay Mehta	USA
Maria Teresa Costantino	Italy	James N. Moy	USA
Giuseppina Cuttitta	Italy	Ugo Nwokoro	USA
Mario di Gioacchino	Italy	Purvi Parikh	USA
Alessandro Fois	Italy	Sudhir Parikh	USA
Maria Pia Foschino-Barbaro	Italy	Frank Perrino	USA
Enrico Gammeri	Italy	James Ruhlmann	USA
Riccardo Inchingolo	Italy	Catherine Sassoon	USA
Federico Lavorini	Italy	Russell A. Settipane	USA
Antonio Molino	Italy	Daniel Sousa	USA
Eleonora Nucera	Italy	Peruvemba Sriram	USA
Alberto Papi	Italy	Richard Wachs	USA
Vincenzo Patella	Italy		
Alberto Pesci	Italy		
Fabio Ricciardolo	Italy		
Paola Rogliani	Italy		
Riccardo Sarzani	Italy		
Carlo Vancheri	Italy		
Rigoletta Vincenti	Italy		

[a]Data for patients from China were excluded from the present analyses due to a change in regulations about data transfer in May 2019.

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