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Prevalence and clinical characteristics of persistent airflow limitation in a cohort of adults with asthma and/or chronic obstructive pulmonary disease

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Abstract

Rationale: **The clinical characteristics of persistent airflow limitation (PAL) were explored in patients aged ≥12 years with physician-assigned diagnoses of asthma, asthma plus chronic obstructive pulmonary disease (COPD), or COPD in the NOVEL Observational longiTudinal studY (NOVELTY) cohort. The NOVELTY study is a prospective study conducted in primary and secondary care in 18 countries.**

Objectives: **To determine the proportion of patients with PAL at baseline, their baseline characteristics, and the stability and prognostic utility of PAL during follow-up.**

Methods: **PAL was defined as post–bronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio less than the lower limit of the normal range (European Respiratory Society [ERS]/American Thoracic Society [ATS]) or as <0.7 (Global Initiative for Chronic Obstructive Lung Disease [GOLD] criteria).**

Results: **We studied 9081 patients over 3 years (asthma: 4754; asthma + COPD; 1147; COPD: 3180). Baseline prevalence of PAL was 24.2% and 29.2% (asthma), 63.3% and 74.1% (asthma + COPD), and 65.4% and 75.8% (COPD) using ERS/ATS and GOLD criteria, respectively. Patients with PAL had markedly worse symptom burden and a history of more frequent moderate and severe exacerbations. In patients with asthma, PAL was associated with higher blood eosinophils and fractional exhaled nitric oxide (FeNO) values; 60% had never smoked. Of patients with PAL at baseline 84% continued to meet PAL criteria at Year 3. Irrespective of physician diagnosis, PAL was a marker of increased risk of moderate and severe exacerbations and poor symptom control during the 3-year follow-up.**

Conclusions: **PAL is a stable trait associated with more severe disease and poor outcomes in adults with a physician-assigned diagnosis of asthma and/or COPD.**

Clinical Trial Registration (if any): **NOVELTY: NCT02760329.**

Keywords asthma, chronic obstructive pulmonary disease, persistent airflow limitation, spirometry, symptoms

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Introduction

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) mandates that, in patients with respiratory symptoms, the diagnosis of chronic obstructive pulmonary disease (COPD) requires the demonstration of a post–bronchodilator (BD) forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio <0.70, traditionally referred to as persistent airflow limitation (PAL).[1,2] After reaching its peak in early adulthood, lung function decreases physiologically with age; therefore, the European Respiratory Society (ERS)/American Thoracic Society (ATS) Taskforce has proposed an alternative criterion to define abnormal airflow obstruction based on a post–BD FEV_1/FVC ratio below the lower limit of the normal (LLN) range, defined as the fifth percentile of a healthy population.[3,4] This criterion should reduce the risk of under–diagnosing PAL in young people and overdiagnosing it in healthy older adults.[5-7]

PAL is not exclusive to COPD. A proportion of children and adults with longstanding asthma may also have PAL.[8-13] In these patients, PAL has been related to increasing age, male sex, longer duration of asthma, a greater history of smoking, genetic variants, higher blood eosinophil count, more small airways dysfunction, and a greater frequency of exacerbations.[8-13]

The term PAL can have 2 meanings that overlap and are not always explicitly identified. Persistent could refer to the presence of an abnormal FEV_1/FVC ratio on multiple occasions over time, or mean that this ratio remains abnormal after inhalation of a BD drug. It is this second characteristic that has traditionally been considered to differentiate patients with asthma from those with COPD, and is the focus of this report.

Here, we investigated the prevalence, associated clinical characteristics, stability, and prognostic utility of PAL in the NOVEL Observational longiTudinal studY (NOVELTY), a large, real–world, global observational study of patients with physician-diagnosed asthma and/or COPD. The primary hypothesis was that the clinical characteristics and outcomes associated with the presence of PAL would be similar between those patients with a physician-assigned diagnosis of asthma or COPD, despite some differences in background exposures. The analyses were conducted using both the ERS/ATS and GOLD criteria for the definition of PAL. This study complements a recent paper that investigated BD responsiveness (BDR) in obstructive airway disease in the same NOVELTY population.[14]

Methods

Study design and ethics

Details of the NOVELTY study design have been reported previously.[15,16] Briefly, NOVELTY is a prospective, non–interventional, observational cohort study of patients with chronic airways disease enrolled from community and hospital outpatient settings in 18 countries. Patients were required to have a diagnosis, or a clinically suspected diagnosis, of asthma and/or COPD according to the treating physician; intentionally, no diagnostic criteria are specified. Patients were recruited between September 2015 and March 2017. Recruitment was stratified by physician-assigned severity, with the aim of similar numbers of recruited patients distributed between the mild, moderate, and severe categories. The NOVELTY study was approved by the institutional review boards of each participating institution, and all patients provided written informed consent.

Participants

The NOVELTY study cohort included 9081 patients who underwent pre– and post–BD spirometry assessment at baseline (Visit 1). Additionally, the number of patients assessed at the follow-up visits were 8108 at Year 1 (12 months), 7219 at Year 2 (24 months), and 6351 at Year 3 (36 months). The patient flow diagram is shown in Figure S1 (see online supplementary material for a color version of this figure) of the online data supplement.

Variables

Variables included demographics, clinical characteristics, healthcare resource utilization, health-related quality of life, symptoms, medications, and biomarkers collected at baseline and at Years 1, 2, and 3 (Table S1).

Spirometry was performed by sites trained to the relevant ERS/ATS standards[17] at baseline and again 15-30 minutes after administration of a BD, with the agent and doses used according to local practice.

Data analysis and outcomes

In this study, PAL was defined as an abnormal FEV_1/FVC ratio (ie, below the cutoff value indicated by the criteria used) following the administration of a BD. PAL was assessed by 2 criteria: (1) PAL (ERS/ATS), post–BD FEV_1/FVC <LLN at baseline, with LLN values for FEV_1 and FVC derived from the ERS Global Lung Function Initiative reference equations[18]; and (2) PAL (GOLD), post–BD FEV_1/FVC <0.7 at baseline.

The primary outcome was the characteristics of patients with PAL at baseline as assessed by these 2 criteria within each physician-assigned diagnosis (asthma, asthma+COPD, or COPD). Secondary outcomes included: (1) proportion of patients with PAL by physician diagnosis; (2) the temporal stability of PAL between baseline and Year 3, and PAL trajectories from baseline to Year 3; and *3)* the longitudinal clinical outcomes in patients with or without PAL within each diagnostic group.

Statistical analyses

Continuous variables are presented as mean (standard deviation [SD]), median, and interquartile range. For categorical variables, denominators for proportions exclude patients with missing data. *P*-values were produced by chi-square tests for categorical variables, by 1-way analysis of variance for normally distributed continuous variables, and Kruskal–Wallis *H*-test for non–normally distributed variables. The nominal *P*-values reported were not adjusted for multiple statistical testing and should be interpreted as exploratory in nature.

Changes in post–BD FEV_1/FVC ratio (the defining characteristic of PAL) over time are presented as alluvial plots. Distributions for each physician diagnosis group (asthma, asthma+COPD, or COPD) and physician-assessed severity (mild, moderate, severe) are represented with bar plots. Associations of PAL with longitudinal outcomes were estimated using negative binomial regression for count outcomes (eg, exacerbations) and logistic regression for binary outcomes; results are presented using forest-like plots

indicating the appropriate association measures (incidence rate ratios and odds ratios, respectively). The associations were examined at baseline (before 12 months) and for each subsequent year of the study by diagnosis, and by diagnosis and physician-assessed severity. Models were adjusted for baseline age, sex, and smoking status.

We defined PAL trajectories for patients with at least 3 measurements from baseline to Year 3. Patients with PAL at all visits were classified as "Stable PAL," those without PAL at any visit as "Stable Not PAL," and those with variable status as "Unstable PAL."

We plotted the mean FEV_1/FVC ratio by study visit for each PAL trajectory by physician diagnosis. Among patients with asthma or COPD, we evaluated characteristics associated with Unstable PAL versus Stable PAL or Stable Not PAL trajectories. Odds ratios were estimated using multinomial models, with each characteristic evaluated as the exposure and PAL trajectory as the outcome, without further adjustment. Additionally, we cross-tabulated any changes in physician diagnosis of asthma and/or COPD during follow-up by PAL trajectory.

Statistical analysis was performed using the R statistical package, version 4.1.0, in Rstudio, version 2021.09.2.

Results

Prevalence of PAL

Of 11 192 patients included in the NOVELTY study, 9081 patients had spirometry measurements and were included in this analysis: 4754 with a physician-assigned diagnosis of asthma, 1147 with asthma + COPD, and 3180 with COPD (Figure S1, see online supplementary material for a color version of this figure). According to the ERS/ATS and GOLD criteria, respectively, the prevalence of PAL was 24.2% and 29.2% in patients with asthma, 63.3% and 74.1% in patients with asthma + COPD, and 65.4% and 75.8% in patients with COPD. PAL was more prevalent in patients with more severe disease (based on physician-assessed severity), irrespective of their assigned diagnosis (Figure 1, Tables 1 and 2, and Table S 2).

Differential clinical characteristics at baseline

The baseline characteristics associated with PAL were consistent whether evaluated by ERS/ATS or GOLD criteria (Tables 1 and 2 and Tables S3 and S4). Overall, patients with PAL were older, more often male, with lower body mass index (BMI), higher prevalence of emphysema and bronchiectasis, greater cumulative tobacco pack-year consumption, and longer duration since diagnosis. They were also more likely to have a history of multiple cardiovascular comorbidities. There were significant differences in the mean post–BD FEV_1 and forced mid-expiratory flow at 25%-75% predicted between patients with PAL and those without PAL, with markedly lower levels observed in PAL (more so for forced mid-expiratory flow at 25%-75%), whereas differences in FVC were small. PAL patients exhibited greater BDR, especially under the 2021 definition that includes both FEV_1 and FVC reversibility (change in FEV_1 or change in FVC BDR >10% pred).[4] With respect to blood biomarkers, patients with PAL had higher monocyte and neutrophil counts, but lower lymphocyte counts. There was no difference in blood eosinophil counts, whereas fractional exhaled nitric oxide (FeNO) was slightly lower. PAL was associated with worse symptoms and quality of life, and a more frequent history of moderate and severe

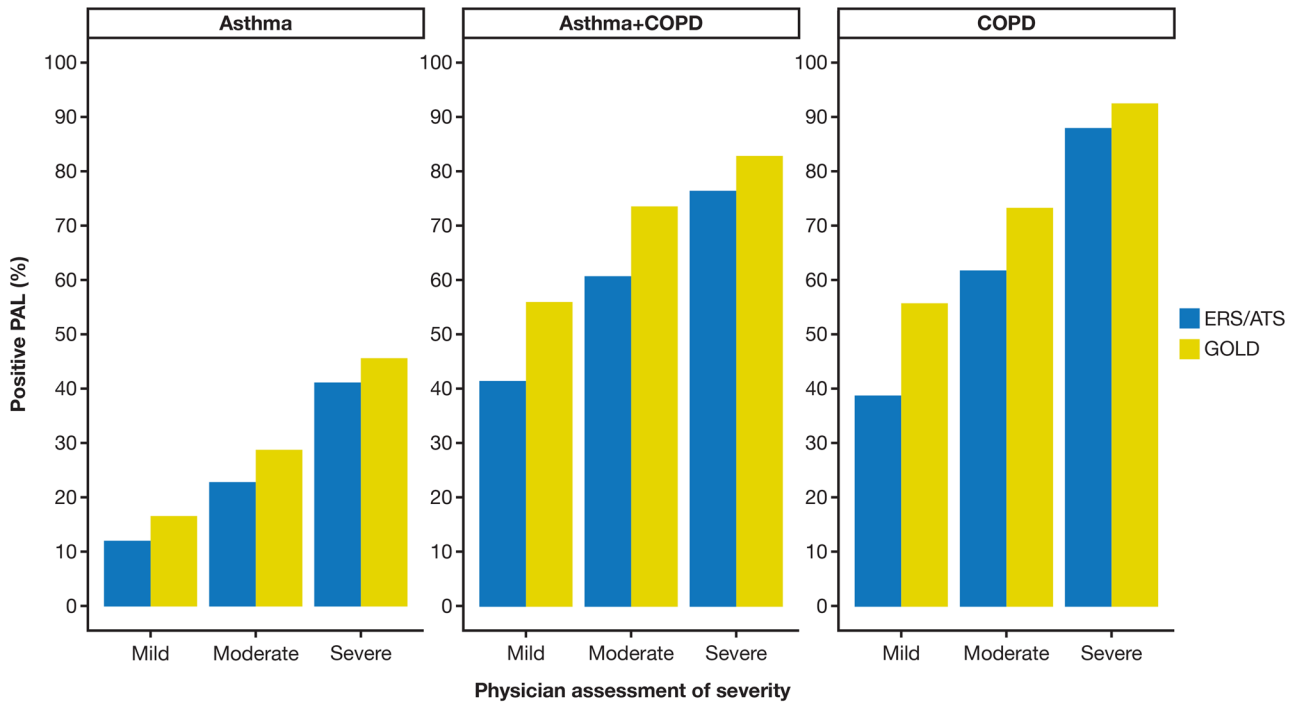

Figure 1 Proportion of patients with PAL in the 3 diagnostic groups, according to physician-assessed severity, by the ERS/ATS and GOLD criteria.

Abbreviations: ATS, American Thoracic Society; COPD, chronic obstructive pulmonary disease; ERS, European Respiratory Society; GOLD, Global Initiative for Chronic Obstructive Lung Disease; PAL, persistent airflow limitation.

Table 1 Clinical characteristics by PAL defined by the ERS/ATS criterion in patients with a physician diagnosis of asthma, asthma + COPD, and COPD.

	Total			Asthma			Asthma + COPD			COPD		
	No PAL (*N* = 5125)	PAL (*N* = 3956)	*P*-value[a]	No PAL (*N* = 3605)	PAL (*N* = 1149)	*P*-value[a]	No PAL (*N* = 421)	PAL (*N* = 726)	*P*-value[a]	No PAL (*N* = 1099)	PAL (*N* = 2081)	*P*-value[a]
Demographics												
Age, years	54.9 (17.0)	63.1 (12.7)	***	50.6 (17.3)	54.9 (16.1)	***	64.4 (10.4)	64.5 (9.9)		65.2 (10.5)	67.1 (8.8)	***
Male	2074 (40.5)	2238 (56.6)	***	1251 (34.7)	508 (44.2)	***	195 (46.3)	393 (54.1)	*	628 (57.1)	1337 (64.2)	***
BMI, kg/m^2	29.0 (7.0)	27.0 (6.0)	***	28.5 (7.0)	27.4 (6.2)	***	30.8 (6.9)	27.7 (6.1)	***	30.0 (6.8)	26.5 (5.8)	***
Current smoker	785 (15.3)	854 (21.6)	***	284 (7.9)	111 (9.7)		113 (26.8)	175 (24.1)		388 (35.3)	568 (27.3)	***
Pack-years	14.1 (25.9)	33.5 (38.8)	***	5.8 (16.8)	7.5 (17.8)	**	26.5 (26.9)	35.1 (32.1)	***	36.5 (33.8)	47.4 (42.0)	***
Diagnosis variables												
Years since diagnosis	15.4 (16.3)	16.0 (17.0)		17.4 (16.4)	25.2 (19.2)	***	20.4 (20.2)	24.0 (21.3)	**	6.8 (9.9)	8.3 (8.0)	***
Age at symptoms onset, yr	35.1 (22.5)	42.1 (22.3)	***	29.3 (20.9)	25.5 (19.7)	***	39.7 (22.3)	35.0 (23.1)	**	52.5 (17.9)	53.7 (15.6)	
Physician severity												
Mild	2211 (43.1)	650 (16.4)	***	1519 (42.1)	207 (18.0)	***	116 (27.6)	82 (11.3)	***	576 (52.4)	361 (17.3)	***
Moderate	1848 (36.1)	1281 (32.4)		1278 (35.5)	378 (32.9)		203 (48.2)	313 (43.1)		367 (33.4)	590 (28.4)	
Severe	1066 (20.8)	2025 (51.2)		808 (22.4)	564 (49.1)		102 (24.2)	331 (45.6)		156 (14.2)	1130 (54.3)	
Select comorbidities												
Emphysema[b]	394 (7.7)	1281 (32.4)	***	58 (1.6)	43 (3.7)	***	79 (18.8)	266 (36.6)	***	257 (23.4)	972 (46.7)	***
Bronchiectasis[b]	211 (4.1)	318 (8.0)	***	126 (3.5)	94 (8.2)	***	39 (9.3)	62 (8.5)		46 (4.2)	162 (7.8)	***
Chronic bronchitis	217 (4.2)	215 (5.4)	**	79 (2.2)	29 (2.5)		47 (11.2)	54 (7.4)		91 (8.3)	132 (6.3)	*
Hypertension	1616 (31.5)	1456 (36.8)	***	876 (24.3)	299 (26.0)		193 (45.8)	257 (35.4)	***	547 (49.8)	900 (43.2)	***
Type 2 diabetes	677 (13.2)	462 (11.7)	*	345 (9.6)	101 (8.8)		84 (20.0)	90 (12.4)	***	248 (22.6)	271 (13.0)	***
CHD	482 (9.4)	559 (14.1)	***	191 (5.3)	72 (6.3)		77 (18.3)	103 (14.2)		214 (19.5)	384 (18.5)	
GERD	834 (16.3)	619 (15.6)		522 (14.5)	200 (17.4)	*	105 (24.9)	137 (18.9)	*	207 (18.8)	282 (13.6)	***
Respiratory medications (available for 90% of patients)												
Reliever only	569 (12.5)	218 (6.0)	***	382 (11.7)	59 (5.4)	***	48 (12.3)	46 (6.6)	**	139 (15.4)	113 (6.0)	***
Any ICS, including combination	3465 (76.3)	2661 (72.9)	***	2740 (84.3)	971 (89.6)	***	282 (72.3)	559 (80.3)	**	443 (49.2)	1131 (60.5)	***
Triple (open/fixed)	590 (13.0)	1412 (38.7)	***	288 (8.9)	267 (24.6)	***	118 (30.3)	345 (49.6)	***	184 (20.4)	800 (42.8)	***
OCS maintenance	84 (1.8)	140 (3.8)	***	74 (2.3)	76 (7.0)	***	6 (1.5)	36 (5.2)	**	4 (0.4)	28 (1.5)	*
Biologics	259 (5.7)	238 (6.5)		245 (7.5)	198 (18.3)	***	14 (3.6)	39 (5.6)		0 (0.0)	1 (0.1)	
Burden (available for indicated % of patients [%])												
Mod/severe exacerbations [100%]	0.4 (0.9)	0.7 (1.3)	***	0.4 (0.9)	0.7 (1.3)	***	0.7 (1.4)	1.0 (1.7)	**	0.3 (0.7)	0.6 (1.1)	***
SGRQ total score [70%]	31.1 (21.1)	41.2 (22.2)	***	28.6 (20.2)	35.9 (22.8)	***	37.8 (23.0)	41.3 (21.3)	*	37.5 (21.3)	44.0 (21.7)	***
CAAT total [71%]	14.3 (8.4)	17.1 (8.5)	***	13.5 (8.2)	15.8 (9.2)	***	17.0 (8.9)	17.3 (8.2)		15.9 (8.3)	17.7 (8.2)	***
Healthcare utilization past 12 months												
Related GP visits	1.6 (2.7)	1.8 (3.0)	***	1.4 (2.6)	1.6 (2.8)	*	2.2 (3.1)	2.6 (3.6)	*	2.0 (3.0)	1.7 (2.8)	**
Specialist visits	2.0 (2.9)	2.5 (3.1)	***	2.3 (3.1)	3.1 (3.7)	***	1.8 (2.6)	2.5 (3.2)	***	1.4 (2.1)	2.2 (2.6)	***

Abbreviations: ATS, American Thoracic Society; CAAT, Chronic Airways Assessment Test; CHD, coronary heart disease (myocardial infarction or congestive heart failure history); COPD, chronic obstructive pulmonary disease; ERS, European Respiratory Society; GERD, gastro-esophageal reflux disease; GP, general practitioner; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; mod, moderate; OCS, oral corticosteroid; PAL, persistent airflow limitation; pred, predicted; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire; yr, years.
Data are presented as *n (%)* for categorical variables and *mean (SD)* for continuous variables. Data were available for all patients unless where specified otherwise.
*P-value is less than 0.05.
**P-value is less than 0.01.
***P-value is less than 0.001.
[a]Wilcoxon rank sum test; Pearson's Chi-squared test.
[b]History of emphysema and bronchiectasis is derived from the medical history documented in the electronic case report form and lung computed tomography records from the medical file.

exacerbations that necessitated systemic corticosteroid use, emergency department visits, or hospitalizations. Reflecting their greater disease burden, patients with PAL were more likely to receive dual and triple inhaler therapy, long-term oral corticosteroids, and biologics (patients with asthma).

Although many of these associations were broadly similar when evaluated within each physician diagnostic group, several differences were observed (Tables 1 and 2 and Tables S5 and S6). Asthma patients with PAL had higher blood eosinophil and FeNO levels and markedly higher BDR (according to both the 2005 and 2021 definitions) compared to asthma patients without PAL; these associations were not observed or were much weaker in COPD or asthma + COPD. In asthma patients, tobacco exposure was relatively low and did not differ much by PAL, whereas there were clear contrasts in the level of exposure to smoking between patients with versus without PAL in COPD and asthma + COPD. Of note, 694/1149 (60%) patients with asthma and PAL had never smoked compared with 12% and 5% in the asthma + COPD and COPD groups, respectively. Although the duration of disease was associated with increased PAL prevalence across all patients, earlier symptoms onset was associated with greater PAL prevalence in asthma and asthma + COPD. In asthma, there was an association between gastro-esophageal reflux disease and PAL that was not observed in the other groups. Finally, the inverse association of PAL with BMI was more pronounced in COPD and asthma + COPD than in asthma and spanned all BMI groups (in asthma, it was confined to obese patients).

Temporal stability and trajectory analysis

Transitions in PAL during follow-up are illustrated in Figure 2. Table 3 shows the temporal stability of PAL (ERS/ATS), as evaluated by cross-tabulation versus the baseline value. Over 84% of patients with PAL at baseline continued to meet PAL criteria at the Year 3 visit. Conversely, 88% of those without PAL at baseline continued to be without PAL at Year 3. PAL was more stable in patients diagnosed with COPD or asthma+COPD (89% remained PAL at Year 3), compared to asthma patients (74% remained PAL at Year 3). Temporal stability was similar for the GOLD criteria (Tables S7 and S8).

A more nuanced picture of PAL stability emerges when examining PAL trajectories across all visits. As shown in Table S9, a substantial proportion of patients (630 with asthma [25%], 156 with asthma + COPD [20%], and 377 with COPD [21%]) demonstrated an Unstable PAL trajectory, indicating that PAL can fluctuate considerably between visits. Baseline characteristics for these trajectories are presented in Table S10. Figure S2 (see online supplementary material for a color version of this figure) shows the mean FEV_1/FVC values by trajectory. Patients with Unstable PAL, particularly those with asthma, tended to have FEV_1/FVC values fluctuating near the 70% threshold over time, whereas values remained well above 70% in the Stable Not PAL group and were consistently lower in the Stable PAL group. Patients with asthma with an Unstable PAL trajectory, as compared to those with a Stable Not PAL trajectory, were diagnosed more recently, and were more likely male, current smokers, with severe disease, worse lung function, and more comorbidities (Table S10 and Figure S3a, see online supplementary material for a color version of this figure). Compared to those with a Stable PAL trajectory, patients with COPD with an Unstable PAL trajectory were more likely to be current smokers, had higher BMI, FeNO, and blood eosinophil counts, had mild disease, had better lung function, and were less frequently prescribed intensive respiratory therapies such as triple therapy or biologics (Table S10 and Figure S3b, see online supplementary material for a color version of this figure). These patterns were generally consistent with baseline comparisons of PAL versus no PAL, although the observed associations with Unstable PAL were weaker.

Evaluation of diagnosis changes over time showed that, regardless of PAL trajectory, physicians' baseline diagnosis remained stable (>96%) for nearly all patients (Table S11). Nonetheless, patients with an Unstable PAL trajectory were somewhat more likely to have their diagnosis revised, most commonly to a dual (asthma + COPD) diagnosis, although transitions to asthma-only or COPD-only were rare and typically occurred among those initially diagnosed with asthma + COPD.

Association of PAL with longitudinal outcomes

The presence of baseline PAL was associated with increased risk of moderate and severe exacerbations, and poor symptom control during follow-up across asthma, asthma+COPD, and COPD (Figures S4-S6, see online supplementary material for a color version of these figures). The baseline characteristics of patients with and without follow-up data were broadly similar (Table S12).

Discussion

This analysis of the NOVELTY study shows that in a large, global, real-life setting, the prevalence of PAL in patients with a diagnosis of asthma was 24%, and in those with a diagnosis of asthma+COPD or COPD was 63% and 65%, respectively, utilizing the ERS/ATS criterion to define PAL. When the GOLD criterion was used instead, the prevalence of PAL was modestly higher across all physician-assigned diagnoses. Patients with PAL were more likely to have multiple cardiovascular comorbidities, markedly worse symptom burden, and more frequent moderate and severe exacerbations. Additionally, in patients diagnosed with asthma, those with PAL had higher blood eosinophil counts and FeNO levels than those without PAL and exhibited greater BD reversibility. Unlike in COPD patients, among whom 95% were current or former smokers, we observed that 60% of asthma patients with PAL had never smoked, underscoring the potential role of factors beyond smoking in the development of PAL in asthma. We found that 84% of patients with PAL at baseline continued to have PAL at the Year 3 visit. Our longitudinal outcomes analysis showed that the presence of PAL at the baseline visit was a marker of increased risk of severe exacerbations and poor symptom control throughout the 3-year follow-up, within and across asthma, COPD, and asthma + COPD. Collectively, these observations show that PAL is an important trait to consider in the clinical management of the heterogeneous population of patients with chronic airway diseases.[19-22]

The GOLD criterion of a post–BD FEV_1/FVC ratio of <0.7 has a practical advantage of being simple to derive in clinical practice and provides good discrimination to identify individuals at risk of clinically significant COPD, predicting both COPD-related hospitalization and mortality.[23] However, this threshold does not ac-

Table 2 Clinical characteristics by PAL defined by the ERS/ATS criterion in patients with a physician diagnosis of asthma, asthma + COPD, and COPD.

	Total			Asthma			Asthma+COPD			COPD		
	No PAL ($N = 5125$)	PAL ($N = 3956$)	*P*-value[a]	No PAL ($N = 3605$)	PAL ($N = 1149$)	*P*-value[a]	No PAL ($N = 421$)	PAL ($N = 726$)	*P*-value[a]	No PAL ($N = 1099$)	PAL ($N = 2081$)	*P*-value[a]
Lung function												
Post–FEV_1, % pred	89.2 (18.3)	58.2 (20.5)	***	93.3 (16.6)	67.3 (19.1)	***	81.7 (18.3)	60.3 (19.3)	***	78.8 (18.4)	52.5 (19.7)	***
Post-FVC, % pred	91.4 (18.1)	87.7 (21.0)	***	94.7 (16.5)	91.3 (19.7)	***	85.9 (18.7)	91.2 (20.3)	***	82.9 (19.3)	84.5 (21.4)	*
Post–FEV_1/FVC, %	78.0 (7.5)	51.4 (11.8)	***	79.6 (7.0)	58.4 (9.4)	***	74.2 (7.0)	51.2 (11.0)	***	74.2 (7.2)	47.6 (11.4)	***
Post FEF 25%-75%, % pred	89.7 (35.9)	35.8 (26.0)	***	94.8 (34.3)	40.5 (23.5)	***	80.2 (38.9)	34.5 (25.5)	***	77.5 (35.7)	33.3 (27.3)	***
BDR (using 2005 or 2021 criteria)												
ΔFEV_1 ≥12% and ≥200 mL (2005)	646 (12.9)	751 (19.9)	***	454 (12.9)	302 (27.5)	***	61 (14.8)	166 (23.7)	***	131 (12.2)	283 (14.4)	
ΔFEV_1 or ΔFVC BDR >10% pred (2021)	669 (13.4)	874 (23.2)	***	499 (14.2)	301 (27.5)	***	49 (11.9)	173 (24.8)	***	121 (11.3)	400 (20.3)	***
Biomarkers (available for indicated % of patients [%])												
FeNO, ppb [89%]	28.2 (26.9)	25.4 (25.1)	***	31.0 (28.8)	35.8 (33.5)	***	23.1 (22.8)	24.9 (23.3)		20.5 (18.3)	19.3 (16.4)	
Blood eosinophils, cells/μL [51%]	204.6 (153.7)	213.0 (191.4)		211.7 (163.1)	266.5 (262.7)	***	203.0 (141.6)	214.7 (196.5)		183.8 (124.7)	182.3 (123.5)	
Blood neutrophils, 10^9/L [51%]	4.5 (1.8)	4.9 (1.9)	***	4.4 (1.7)	4.7 (2.1)	***				4.8 (1.9)	5.0 (1.8)	
Blood lymphocytes, 10^9/L [51%]	2.0 (0.7)	1.9 (0.7)	***	2.0 (0.7)	1.9 (0.7)	*	2.1 (0.8)	2.0 (0.8)		2.1 (0.7)	1.9 (0.7)	***
Blood monocytes, 10^9/L [51%]	0.4 (0.2)	0.5 (0.2)	***	0.4 (0.2)	0.4 (0.2)	**	0.5 (0.2)	0.5 (0.2)		0.4 (0.2)	0.5 (0.2)	**

Abbreviations: ATS, American Thoracic Society; BDR, bronchodilator responsiveness; COPD, chronic obstructive pulmonary disease; ERS, European Respiratory Society; FEF, forced mid-expiratory flow; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced viral capacity; PAL, persistent airflow limitation; pred, predicted; SD, standard deviation.
Data are presented as *n (%)* for categorical variables and *mean (SD)* for continuous variables. Data were available for all patients unless where specified otherwise.
*P-value is less than 0.05.
**P-value is less than 0.01.
***P-value is less than 0.001.
[a]Wilcoxon rank sum test; Pearson's Chi-squared test.

Table 3 Cross tabulation of PAL at baseline versus years 1-3, by disease diagnosis, according to the ERS/ATS criterion.

PAL	No PAL at baseline (*N* = 5125)	PAL at baseline (*N* = 3956)
Overall		
Year 1		
No PAL	3506/3993 (87.8)	397/3139 (12.6)
PAL	487/3993 (12.2)	2742/3139 (87.4)
Missing	1132	817
Year 2		
No PAL	2715/3055 (88.9)	331/2323 (14.2)
PAL	340/3055 (11.1)	1992/2323 (85.8)
Missing	2070	1633
Year 3		
No PAL	1835/2091 (87.8)	256/1625 (15.8)
PAL	256/2091 (12.2)	1369/1625 (84.2)
Missing	3034	2331
Asthma		
Year 1		
No PAL	2570/2850 (90.2)	193/931 (20.7)
PAL	280/2850 (9.8)	738/931 (79.3)
Missing	755	218
Year 2		
No PAL	2008/2196 (91.4)	160/696 (23.0)
PAL	188/2196 (8.6)	536/696 (77.0)
Missing	1409	453
Year 3		
No PAL	1364/1518 (89.9)	132/506 (26.1)
PAL	154/1518 (10.1)	374/506 (73.9)
Missing	2087	643
Asthma+COPD		
Year 1		
No PAL	256/320 (80.0)	49/591 (8.3)
PAL	64/320 (20.0)	542/591 (91.7)
Missing	101	135
Year 2		
No PAL	222/266 (83.5)	51/474 (10.8)
PAL	44/266 (16.5)	423/474 (89.2)
Missing	155	252
Year 3		
No PAL	153/179 (85.5)	35/318 (11.0)
PAL	26/179 (14.5)	283/318 (89.0)
Missing	242	408
COPD		
Year 1		
No PAL	680/823 (82.6)	155/1617 (9.6)
PAL	143/823 (17.4)	1462/1617 (90.4)
Missing	276	464
Year 2		
No PAL	485/593 (81.8)	120/1153 (10.4)
PAL	108/593 (18.2)	1033/1153 (89.6)
Missing	506	928
Year 3		
No PAL	318/394 (80.7)	89/801 (11.1)
PAL	76/394 (19.3)	712/801 (88.9)
Missing	705	1280

Abbreviations: ATS, American Thoracic Society; COPD, chronic obstructive pulmonary disease; ERS, European Respiratory Society; PAL, persistent airflow limitation.
Values are presented as *n* (%), unless stated otherwise.

count for the influence of age, sex, and ethnicity on lung function[17] and, in particular, that the FEV_1/FVC ratio decreases by an estimated 0.29% per year, as part of the normal lung aging process.[24] This has led to the joint ERS/ATS Task Force criterion using the alternative cut-off value for the FEV_1/FVC ratio set at the fifth percentile of the normal distribution, rather than at a fixed value of 0.7.[3] This more stringent ERS/ATS criterion, which has its own limitations in terms of derivation of normal reference ranges in different populations for application to all individuals, explains our observation that the prevalence of PAL was lower with the ERS/ATS compared with the GOLD criteria, as reported previously.[25]

It may seem paradoxical that some patients were classified as having COPD despite having FEV_1/FVC ratios greater than 0.7 and above the LLN. However, in this study, we have classified patients based on the diagnosis provided by their attending physician rather than solely relying on FEV_1/FVC cutoffs, to reflect the diagnoses found in clinical practice. Additionally, lung function can fluctuate over time, and our 3-year longitudinal data demonstrate that some patients may move in and out of formal diagnostic criteria.[26] Notably, although diagnostic labels remained stable for most patients, those with an Unstable PAL trajectory were more likely to have their diagnoses revised over time, most commonly by the addition of a dual asthma + COPD diagnosis. These findings extend the observation that asthma + COPD has an intermediate position on an asthma-to-COPD gradient.[27]

The observation that approximately one-quarter of patients with a diagnosis of asthma had PAL confirms previous observations[28] suggesting that a substantial proportion of patients with asthma progress to develop PAL, not only in those with severe disease, but also in a considerable proportion of those considered to have milder disease according to their treating physician.

There were numerous differences in patient characteristics based on PAL presence in the overall study population of obstructive airways disease, supporting the inclusion of PAL as a distinct trait in airways disease,[29] and raising the possibility that PAL may comprise multiple traits across the heterogeneity of obstructive airways disease. The individual characteristics can be viewed from many perspectives. The observation that those with PAL were more likely to be male, older, have a greater tobacco pack-year consumption, and longer disease duration indicates a pathogenic role of cumulative irritant exposures over time. The greater prevalence of multiple cardiovascular comorbidities with PAL may relate to the common risk factors such as tobacco smoking, male sex, and age, as well as the potential role of impaired lung function as a risk factor for cardiovascular disease and all-cause mortality.[30,31] Patients with PAL had markedly worse measures of pre– and post–BD lung function, as expected by the definitions that are used to define PAL. Consistent with being defined by more severe airflow obstruction, PAL was associated with worse symptom burden and quality of life, and more frequent moderate and severe exacerbations, including emergency department visits and hospital admissions.

Patients with PAL had higher blood neutrophil and monocyte counts but lower lymphocyte counts, which indicates potential roles in pathogenesis or disease progression.[32] The higher blood eosinophil level and FeNO with PAL were limited to the asthma group, consistent with evidence of differences in airways inflammation in patients with PAL due to asthma and COPD.[33,34] It also

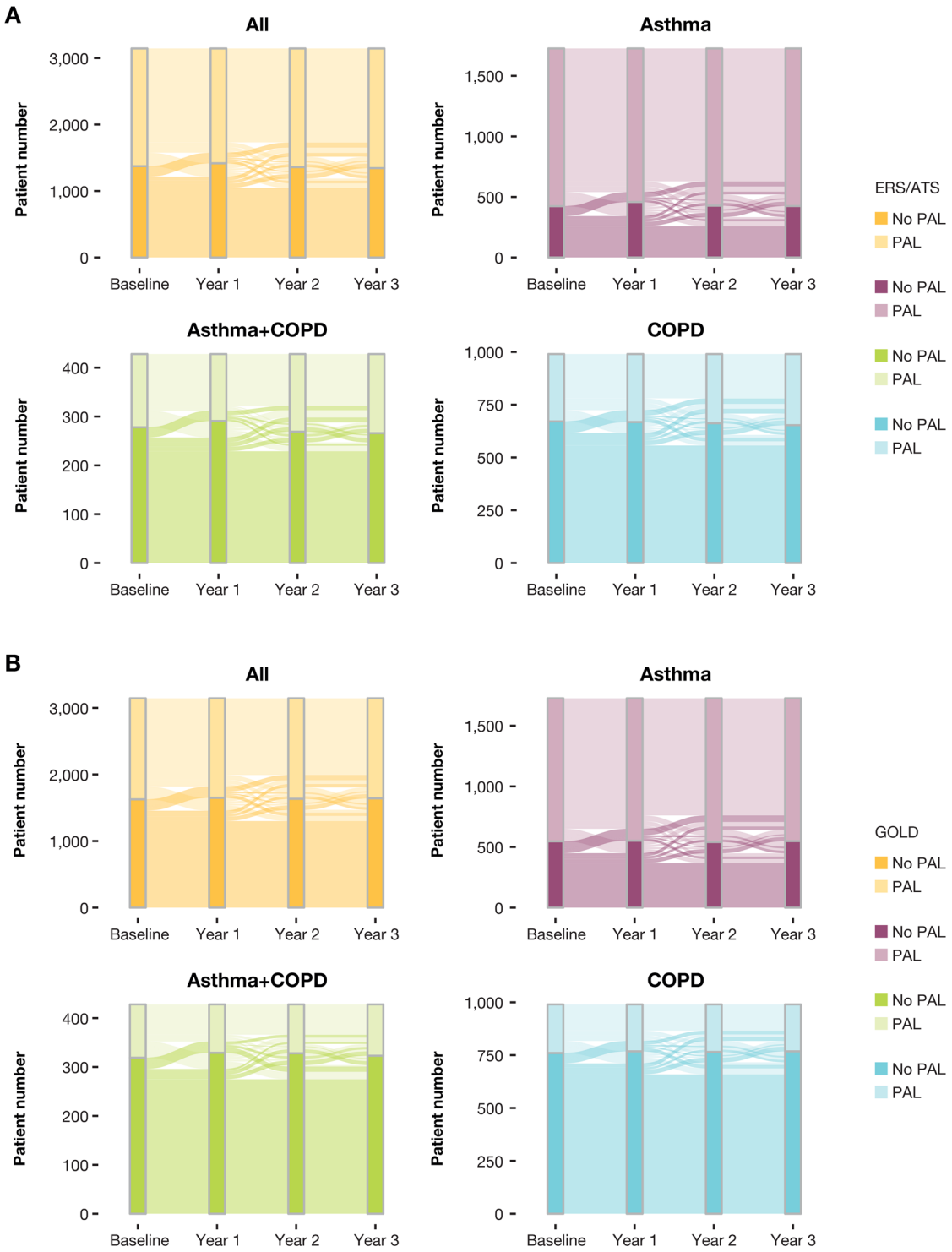

Figure 2 Alluvial plots of PAL presence during 3 years of follow-up in the overall obstructive airways group according to (A) ERS/ATS and (B) GOLD criteria.

Abbreviations: ATS, American Thoracic Society; COPD, chronic obstructive pulmonary disease; ERS, European Respiratory Society; GOLD, Global Initiative for Chronic Obstructive Lung Disease; PAL, persistent airflow limitation.

suggests differing pathogenesis of PAL between diagnostic groups and raises the possibility that PAL may be a marker of multiple pathogenic traits within the range of chronic airways obstructive disease. These concepts are supported by our observation that 60% of asthma patients with PAL had never smoked, compared with 12% and 5% in the asthma + COPD and COPD groups, respectively.

The inverse association we observed between PAL and BMI is well-documented in the literature.[35]It has led to concerns that airflow obstruction may go underdiagnosed among overweight and obese patients.[36] It may also partly explain the development of the Preserved Ratio Impaired Spirometry with Symptoms phenotype, which is more often encountered

among obese patients.[37] Undoubtedly, the relationship of PAL with BMI is complex, and to gain a clearer understanding, we may need to consider a broader range of anthropometric measurements beyond BMI.

In patients with COPD or asthma+COPD, PAL was maintained during the 3-year follow-up, as 84% of those with PAL at baseline continued to meet the ERS/ATS PAL criteria at the Year 3 visit. In contrast, among patients with asthma, PAL was less stable, with over 25% of those who had PAL at baseline no longer meeting the criterion by Year 3. PAL trajectories reveal further heterogeneity in the persistence of PAL over time. Unstable PAL trajectories were observed in roughly one-quarter of patients across all diagnostic groups, with patients with asthma in this group frequently displaying FEV_1/FVC values near the diagnostic threshold—highlighting how reliance on a categorical FEV_1/FVC cut-off may misclassify individuals whose values fluctuate over time. Furthermore, some individuals can have respiratory symptoms and/or structural lesions such as emphysema, and/or physiological abnormalities such as gas trapping, hyperinflation, or reduced lung diffusing capacity, even when categorical thresholds are not met.[1,2] These findings underscore the value of repeated lung function assessment, particularly for patients with borderline values or persistent symptoms.

Given that COPD is clinically diagnosed by the presence of PAL, we compared patients with Unstable PAL to those with Stable Not PAL in asthma and to those with Stable PAL in COPD. For asthma, the association of Unstable PAL with more severe disease, recent diagnosis, ongoing smoking, and greater comorbidity burden underscores the need for comprehensive assessment of risk factors and comorbidities. Conversely, in COPD, Unstable PAL appears linked to features such as higher BMI, mild disease, and elevated FeNO and eosinophil counts—traits that could indicate a more dynamic underlying airway inflammation or a greater potential for disease modification. These findings further emphasize the need to treat patients based on their presenting phenotypes—considering trajectories over time rather than relying solely on one-time values or diagnoses in order to optimize outcomes.

Upon examining associations with long-term outcomes, our findings confirm the utility of PAL as part of a risk assessment across the spectrum of obstructive lung disease, regardless of severity. Over the 3-year follow-up period, the presence of PAL was linked to worse lung function, a greater symptom burden, and a higher risk of moderate and severe exacerbations compared to patients without PAL. An important clinical consideration is that some landmark randomized controlled trials,[38-42] which have subsequently formed the basis of COPD treatment guidelines, used a post–BD FEV_1/FVC ratio of <0.7 as a key inclusion criterion, meaning that there is not a satisfactory evidence base for the management of COPD patients without PAL, as they were not included in these trials. This may represent a sizeable group, as PAL was not present in approximately one-third to one-quarter of patients with a diagnosis of asthma + COPD or COPD, across the range of documented severity. This included those graded as having clinically mild disease, who may have exacerbations, activity limitation, and evidence of structural abnormalities.[43,44] Determining the benefit/risk profile of treatments for patients diagnosed with COPD or asthma+COPD, without PAL, is a priority.

Strengths and weaknesses

This analysis has similar strengths and weaknesses to the companion NOVELTY analysis of BDR.[14] The study had substantive power with >9000 predominantly adult patients and wide generalizability with patients recruited from both primary and secondary care in 18 countries. The diagnostic groups were based on the treating physicians' diagnosis or suspected diagnosis of asthma and/or COPD. Sensitivity analyses, based on more stringent criteria to define subgroups with a high-likelihood diagnosis of asthma and of COPD, showed similar results to the broader diagnostic criteria. We have undertaken multiple statistical comparisons; therefore, those not directly related to the primary outcomes can be considered exploratory. Another limitation is that we have defined PAL by dichotomizing a continuous variable. More insights may be derived by examining different levels of airways obstruction. However, this was not within the scope of the current analysis. We did not have data on trajectories of lung function in childhood or early adult life and so were unable to investigate the role of impairment of lung function during this stage of life, a known predictor of risk of PAL in later adult life.[45,46]

Conclusion

PAL, the presence of persisting airways obstruction despite administration of a BD, is found in approximately one-quarter of treated patients with asthma, and in approximately two-thirds of those treated for asthma + COPD, or COPD, in a real-life setting. The observation that PAL is associated with a greater prevalence of multiple cardiovascular comorbidities, markedly worse lung function and symptom burden, and more frequent moderate and severe exacerbations indicates the importance of recognizing this trait in clinical practice. The observations that most patients with a diagnosis of asthma who had PAL had never smoked, and that in the asthma group PAL was associated with higher blood eosinophil and FeNO values, are both of mechanistic and clinical importance.

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Author contributions

Conceptualization: All authors; Data curation: Eleni Rapsomaniki; Formal analysis: Eleni Rapsomaniki; Funding acquisition: Rod Hughes, Hana Mullerova; Investigation: Rod Hughes (wrote the

original SAP), all authors; Methodology: Rod Hughes, Eleni Rapsomaniki and Richard Beasley (leads); all authors; Project administration: Richard Beasley, Helen Reddel and Alberto Papi (leads); Resources: all authors; Software: R version 4.1.0 Supervision: Richard Beasley, Helen Reddel and Alberto Papi (leads); Validation: Anastasios Mangelis; Visualization: Eleni Rapsomaniki; Writing – original draft: Richard Bealey and Eleni Rapsomaniki; Writing – review & editing: All authors.

Supplementary material

Supplementary material is available at *Annals of the American Thoracic Society* online.

Conflicts of interest

Please see the ICMJE disclosure forms, which have been provided as supplementary material. Richard Beasley has received research grants from AstraZeneca, Teva and HRC (NZ); personal fees from AstraZeneca, Avillion and Teva, is the Chair of the adolescent and adult asthma guidelines group for the Asthma and Respiratory Foundation of New Zealand, and was a former member of the GOLD board. Rod Hughes was an employee of, and held stock in AstraZeneca, and is currently an employee of MSD. Alvar Agustí has received personal fees from AstraZeneca, Chiesi, GSK, Menarini, MSD and Zambon; and has a leadership role on the GOLD board. Peter Calverley has received personal fees from GSK, Sanofi Regeneron, Edmond Pharma, Glenmark and Phillips Respironics and chaired Data Safety Monitoring Boards for Novartis and Genentech. Bradley Chipps has received personal fees from AstraZeneca, Regeneron, and Sanofi Genzyme. Ricardo del Olmo has received research grants from GSK, Sanofi Genzyme and Boehringer Ingelheim, and personal fees from AstraZeneca, Boehringer Ingelheim, Gador, GSK, and Sanofi Genzyme. Alberto Papi received research grants from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Pfizer, Sanofi and Teva; consulting fees from AstraZeneca, Avillion, Chiesi, Elpen Pharmaceuticals, GSK, IQVIA, Novartis and Sanofi; and payment or honoraria from AstraZeneca, Avillion, Boehringer Ingelheim, Chiesi, Edmond Pharma, Elpen Pharmaceuticals, GSK, IQVIA, Menarini, MSD, Mundipharma, Novartis, Sanofi, Teva and Zambon. David Price reports grants or contracts from AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Novartis, Regeneron Pharmaceuticals, the Respiratory Effectiveness Group, Sanofi, Theravance, and the UK National Health Service; reports consulting fees from Airway Vista Secretariat, AstraZeneca, Boehringer Ingelheim, Chiesi, EPG Communication Holdings Ltd, FIECON Ltd, Fieldwork International, GlaxoSmithKline, Mundipharma, Mylan, Novartis, OM Pharma SA, PeerVoice, Phadia AB, Spirosure, Inc, Strategic North Ltd, Synapse Research Management Partners S.L., Talos Health Solutions, Theravance, and WebMD Global LLC; received payment or honoraria from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mundipharma, Mylan, Novartis, Regeneron Pharmaceuticals, and Sanofi; received support for meeting attendance from AstraZeneca, Boehringer Ingelheim, Mundipharma, Mylan, Novartis, and Thermo Fisher; has advisory board membership for AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Novartis, Regeneron Pharmaceuticals, Sanofi, and Thermo Fisher; has stock or stock options in AKL Research and Development Ltd, Observational and Pragmatic Research Institute Pte Ltd (Singapore), and Optimum Patient Care Ltd (Australia and United Kingdom) and 5% shareholding in Timestamp; and is a peer reviewer for grant committees on the UK NIHR Efficacy and Mechanism Evaluation and Health Technology Assessment programs. Hiromasa Inoue has received research grants from Boehringer-Ingelheim, GlaxoSmithKline, Omron, personal fees from AstraZeneca, Boehringer-Ingelheim, GSK, Kyorin, Novartis, Sanofi and is a member of the Global Initiative for Asthma (GINA) Science Committee and Board of Directors. Christer Janson has received research grants from AstraZeneca and GSK and personal fees from AstraZeneca, ALK, Chiesi, GSK, Orion, Sanofi and Stallergenes Maarten van den Berge received research grants from Genentech, GSK, Roche and Sanofi. Helen Reddel received research grants from AstraZeneca, GSK, Perpetual Philanthropy Sanofi and Chiesi; and personal fees from Alkem, AstraZeneca, Boehringer Ingelheim, Chiesi, Getz, GSK, Novartis, Sanofi, and Teva; and has a leadership role in the Australian National Asthma Council and the Global Initiative for Asthma (Chair of Science Committee and member of Board of Directors). Hana Müllerova is an employee and shareholder of AstraZeneca. Anastasios Mangelis is an employee of Phastar Inc Eleni Rapsomaniki is an employee and shareholder of AstraZeneca.

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Data availability

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available, outlining further details: https://vivli.org/ourmember/astrazeneca/. The NOVELTY protocol is available at https://astrazenecagrouptrials.pharmacm.com.

Artificial intelligence disclaimer

No artificial intelligence tools were used in writing this manuscript.

References

1. Global Initiative for Chronic Obstructive Lung Disease. *The Global Initiative of Obstructive Lung Disease (GOLD) Report 2025*. 2024. Accessed November 29, 2024. https://goldcopd.org/2025-gold-report/
2. Agustí A, Celli BR, Criner GJ, et al. Global initiative for chronic obstructive lung disease 2023 report: GOLD executive summary. *Am J Respir Crit Care Med*. 2023;207:819-837. https://doi.org/10.1164/rccm.202301-0106PP

3. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J*. 2005;26:948-968. https://doi.org/10.1183/09031936.05.00035205
4. Stanojevic S, Kaminsky DA, Miller MR, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. *Eur Respir J*. 2022;60:2101499. https://doi.org/10.1183/13993003.01499-2021
5. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society. *Am Rev Respir Dis*. 1991;144:1202-1218.
6. van Dijk W, Tan W, Li P, et al. CanCOLD Study Group. Clinical relevance of fixed ratio vs lower limit of normal of FEV1/FVC in COPD: patient-reported outcomes from the CanCOLD cohort. *Ann Fam Med.* 2015;13:41-48. https://doi.org/10.1370/afm.1714
7. Güder G, Brenner S, Angermann CE, et al. GOLD or lower limit of normal definition? A comparison with expert-based diagnosis of chronic obstructive pulmonary disease in a prospective cohort-study. *Respir Res*. 2012;13:13. https://doi.org/10.1186/1465-9921-13-13
8. Bennett GH, Carpenter L, Hao W, Song P, Steinberg J, Baptist AP. Risk factors and clinical outcomes associated with fixed airflow obstruction in older adults with asthma. *Ann Allergy Asthma Immunol*. 2018;120:164-168.e161. https://doi.org/10.1016/j.anai.2017.10.004
9. Kole TM, Vanden Berghe E, Kraft M, et al. CADSET investigators. Predictors and associations of the persistent airflow limitation phenotype in asthma: a post-hoc analysis of the ATLANTIS study. *Lancet Respir Med*. 2023;11:55-64. https://doi.org/10.1016/S2213-2600(22)00185-0
10. Sousa AW, Barros Cabral AL, Arruda Martins M, Carvalho CRF. Risk factors for fixed airflow obstruction in children and adolescents with asthma: 4-year follow-up. *Pediatr Pulmonol*. 2020;55:591-598. https://doi.org/10.1002/ppul.24625
11. Smith BM, Zhao N, Olivenstein R, Lemiere C, Hamid Q, Martin JG. Asthma and fixed airflow obstruction: long-term trajectories suggest distinct endotypes. *Clin Exp Allergy*. 2021;51:39-48. https://doi.org/10.1111/cea.13714
12. Lee T, Lee YS, Bae Y-J, et al. Smoking, longer disease duration and absence of rhinosinusitis are related to fixed airway obstruction in Koreans with severe asthma: findings from the COREA study. *Respir Res*. 2011;12:1. https://doi.org/10.1186/1465-9921-12-1
13. McGeachie MJ, Yates KP, Zhou X, et al. CAMP Research Group. Genetics and genomics of longitudinal lung function patterns in individuals with asthma. *Am J Respir Crit Care Med*. 2016;194:1465-1474. https://doi.org/10.1164/rccm.201602-0250OC
14. Beasley R, Hughes R, Agusti A, et al. Prevalence, diagnostic utility and associated characteristics of bronchodilator responsiveness. *Am J Respir Crit Care Med*. 2024;209:390-401. https://doi.org/10.1164/rccm.202308-1436OC
15. Reddel HK, Gerhardsson de Verdier M, Agustí A, et al. Prospective observational study in patients with obstructive lung disease: NOVELTY design. *ERJ Open Res*. 2019;5:00036-02018. https://doi.org/10.1183/23120541.00036-2018
16. Reddel HK, Vestbo J, Agustí A, et al. Heterogeneity within and between physician-diagnosed asthma and/or COPD: NOVELTY cohort. *Eur Respir J*. 2021;58:2003927. https://doi.org/10.1183/13993003.03927-2020
17. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26:319-338. https://doi.org/10.1183/09031936.05.00034805
18. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40:1324-1343. https://doi.org/10.1183/09031936.00080312
19. Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J*. 2016;47:410-419. https://doi.org/10.1183/13993003.01359-2015
20. Agustí A, Bafadhel M, Beasley R, et al. Precision medicine in airway diseases: moving to clinical practice. *Eur Respir J*. 2017;50:1701655. https://doi.org/10.1183/13993003.01655-2017
21. Pavord ID, Beasley R, Agusti A, et al. After asthma: redefining airways diseases. *Lancet*. 2018;391:350-400. https://doi.org/10.1016/S0140-6736(17)30879-6
22. McDonald VM, Fingleton J, Agusti A, et al. Treatable traits: a new paradigm for 21st century management of chronic airway diseases: treatable traits down under international workshop report. *Eur Respir J*. 2019;53:1802058. https://doi.org/10.1183/13993003.02058-2018
23. Bhatt SP, Balte PP, Schwartz , JEJr., et al. Discriminative accuracy of FEV1: FVC thresholds for COPD-related hospitalization and mortality. *JAMA*. 2019;321:2438-2447. https://doi.org/10.1001/jama.2019.7233
24. Thomas ET, Guppy M, Straus SE, Bell KJL, Glasziou P. Rate of normal lung function decline in ageing adults: a systematic review of prospective cohort studies. *BMJ Open*. 2019;9:e028150. https://doi.org/10.1136/bmjopen-2018-028150
25. Shirtcliffe P, Weatherall M, Marsh S, et al. COPD prevalence in a random population survey: a matter of definition. *Eur Respir J*. 2007;30:232-239. https://doi.org/10.1183/09031936.00157906
26. Schermer TR, Robberts B, Crockett AJ, et al. Should the diagnosis of COPD be based on a single spirometry test? *NPJ Prim Care Respir Med*. 2016;26:16059. https://doi.org/10.1038/npjpcrm.2016.59
27. Bourdin A, Suehs CM, Marin G, et al. COBRA Consortium. Asthma, COPD, and overlap in a national cohort: ACO on a gradient. *J Allergy Clin Immunol*. 2018;141:1516-1518. https://doi.org/10.1016/j.jaci.2017.11.049
28. Agustí A, Hughes R, Rapsomaki E, et al. The many faces of COPD in real life: a longitudinal analysis of the NOVELTY cohort. *ERJ Open Res*. 2024;10:00895-02023. https://doi.org/10.1183/23120541.00895-2023
29. Agustí A, Rapsomaniki E, Beasley R, et al. Treatable traits in the NOVELTY study. *Respirology*. 2022;27:929-940. https://doi.org/10.1111/resp.14325
30. Ching SM, Chia YC, Lentjes MAH, Luben R, Wareham N, Khaw KT. FEV1 and total cardiovascular mortality and morbidity over an 18 years follow-up population-based prospective EPIC-NORFOLK study. *BMC Public Health*. 2019;19:501. https://doi.org/10.1186/s12889-019-6818-x
31. Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ*. 1996;313:711-715. https://doi.org/10.1136/bmj.313.7059.711discussion 715–716.

32. Ellingsen J, Janson C, Bröms K, et al. Neutrophil-to-lymphocyte ratio, blood eosinophils and COPD exacerbations: a cohort study. *ERJ Open Res*. 2021;7:00471-02021. https://doi.org/10.1183/23120541.00471-2021
33. Fabbri LM, Romagnoli M, Corbetta L, et al. Differences in airway inflammation in patients with fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2003;167:418-424. https://doi.org/10.1164/rccm.200203-183OC
34. Contoli M, Baraldo S, Marku B, et al. Fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease: 5-year follow-up. *J Allergy Clin Immunol*. 2010;125:830-837. https://doi.org/10.1016/j.jaci.2010.01.003
35. Knox-Brown B, Patel J, Potts J, et al. Small airways obstruction and its risk factors in the burden of obstructive lung disease (BOLD) study: a multinational cross-sectional study. *Lancet Glob Health*. 2023;11:e69-e82. https://doi.org/10.1016/S2214-109X(22)00456-9
36. Ço Y, Marott JL, Vestbo J, Lange P. Overweight and obesity may lead to under-diagnosis of airflow limitation: findings from the copenhagen city heart study. *COPD*. 2015;12:5-13. https://doi.org/10.3109/15412555.2014.933955
37. Higbee DH, Granell R, Davey Smith G, Dodd JW. Prevalence, risk factors, and clinical implications of preserved ratio impaired spirometry: a UK biobank cohort analysis. *Lancet Respir Med*. 2022;10:149-157. https://doi.org/10.1016/S2213-2600(21)00369-6
38. Calverley PMA, Anzueto AR, Carter K, et al. Tiotropium and olodaterol in the prevention of chronic obstructive pulmonary disease exacerbations (DYNAGITO): a double-blind, randomised, parallel-group, active-controlled trial. *Lancet Respir Med*. 2018;6:337-344. https://doi.org/10.1016/S2213-2600(18)30102-4
39. Lipson DA, Barnhart F, Brealey N, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med.* 2018;378:1671-1680. https://doi.org/10.1056/NEJMoa1713901
40. Rabe KF, Martinez FJ, Ferguson GT, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *N Engl J Med*. 2020;383:35-48. https://doi.org/10.1056/NEJMoa1916046
41. Vogelmeier C, Hederer B, Glaab T, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. *N Engl J Med*. 2011;364:1093-1103. https://doi.org/10.1056/NEJMoa1008378
42. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359:1543-1554. https://doi.org/10.1056/NEJMoa0805800
43. Woodruff PG, Barr RG, Bleecker E, et al. Clinical significance of symptoms in smokers with preserved pulmonary function. *N Engl J Med*. 2016;374:1811-1821. https://doi.org/10.1056/NEJMoa1505971
44. Ritchie AI, Donaldson GC, Hoffman EA, et al. Structural predictors of lung function decline in young smokers with normal spirometry. *Am J Respir Crit Care Med*. 2024;209:1208-1218. https://doi.org/10.1164/rccm.202307-1203OC
45. Lange P, Celli B, Agustí A, et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. *N Engl J Med*. 2015;373:111-122. https://doi.org/10.1056/NEJMoa1411532
46. McGeachie MJ, Yates KP, Zhou X, et al. Patterns of growth and decline in lung function in persistent childhood asthma. *N Engl J Med*. 2016;374:1842-1852. https://doi.org/10.1056/NEJMoa1513737

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