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Original Research

Frequent productive cough: Symptom burden and future exacerbation risk among patients with asthma and/or COPD in the NOVELTY study

Rod Hughes [a,*], Eleni Rapsomaniki [b], Christer Janson [c], Christina Keen [d], Barry J. Make [e], Pierre-Régis Burgel [f,g], Erin L. Tomaszewski [h], Hana Müllerová [i], Helen K. Reddel [j], on behalf of the NOVELTY study investigators

[a] Research and Early Development, Respiratory and Immunology, Clinical, AstraZeneca, Cambridge, UK
[b] Real World Data Science, BioPharmaceuticals Medical, AstraZeneca, Cambridge, UK
[c] Department of Medical Sciences: Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden
[d] Research and Early Development, Respiratory & Immunology, Clinical, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden
[e] National Jewish Health and University of Colorado Denver, Denver, CO, USA
[f] Department of Respiratory Medicine, Cochin Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France
[g] Université de Paris, Institut Cochin, Inserm U1016, Paris, France
[h] Patient Centered Science, BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, MD, USA
[i] Respiratory & Immunology, Medical and Payer Evidence, BioPharmaceuticals Medical, AstraZeneca, Cambridge, UK
[j] The Woolcock Institute of Medical Research and the University of Sydney, Sydney, Australia

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ABSTRACT

Introduction: Persistent cough with sputum production is an important clinical trait in chronic obstructive pulmonary disease (COPD). We defined "frequent productive cough" based on 2 questions from the St George's Respiratory Questionnaire (SGRQ) and sought to determine its occurrence and associated outcomes in patients with physician-assigned asthma and/or COPD from the NOVELTY study.

Methods: Frequent productive cough was defined as cough and sputum production most or several days/week for the past 3 months (scoring ≥3 for both SGRQ questions). Relationships with baseline disease characteristics and exacerbations over 12 months' follow-up were examined using logistic regression.

Results: Baseline SGRQ data were available for 7125 patients, of whom 31.3% had frequent productive cough. It was more common in asthma+COPD (38.8%) and COPD (38.1%) than asthma (25.0%), increasing with physician-assessed severity, and in current versus former and never smokers. Patient-reported symptomatic worsening was more common in patients with versus without frequent productive cough. Reduced post-bronchodilator FEV_1 (odds ratio [OR] per 10% decrement 1.14 [95% confidence interval 1.11–1.16]) and history of pollutant exposure at home/work (OR 1.50 [1.33–1.69]) were associated with frequent productive cough in all diagnoses. Patients with baseline frequent productive cough were more likely to have ≥1 exacerbation over the subsequent 12 months (OR 1.71 [1.52–1.93]), including exacerbations requiring hospital admission and those treated with oral corticosteroids.

Conclusions: Frequent productive cough represents an important indicator of adverse clinical outcomes across asthma and/or COPD. Research into the underlying pathologic mechanisms is required to support targeted therapy development.

Clinicaltrials.gov: NCT02760329.

1. Introduction

Respiratory symptoms such as shortness of breath, chest tightness, cough, and sputum are common among patients with obstructive lung diseases [1,2], but these symptoms are not specific to either asthma or chronic obstructive pulmonary disease (COPD). The combination of chronic cough and sputum production, described as chronic bronchitis, was recognized in the 1959 Ciba Foundation symposium [3] and over the following years [4] as present in both asthma and emphysema. Subsequently, chronic bronchitis was formally defined as persistent cough with sputum production for at least 3 months of the year, in at least 2 consecutive years [5,6]. More recently, in patients with COPD,

* Corresponding author. AstraZeneca PLC, Melbourne Science Park, Royston, SG8 6HB, UK.
E-mail address: rod.hughes@astrazeneca.com (R. Hughes).

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List of abbreviations

ATS	American Thoracic Society
BMI	body mass index
CAPTURE	COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk
CHD	coronary heart disease
CI	confidence interval
COPD	chronic obstructive pulmonary disease
ED	emergency department
ERS	European Respiratory Society
FeNO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in 1 s
FPC	frequent productive cough
FVC	forced vital capacity
GERD	gastroesophageal reflux disease
LLN	lower limit of normal
NOVELTY	NOVEL observational longiTudinal studY
OCS	oral corticosteroids
OR	odds ratio
ppb	parts per billion
SD	standard deviation
SGRQ	St George's Respiratory Questionnaire

chronic cough and sputum production have been associated with lung function decline, exacerbation risk, and increased risk of mortality [7–10]. Patients with COPD who have symptoms of chronic bronchitis typically have more respiratory symptoms, more frequent exacerbations, and worse clinical trajectories than those without chronic bronchitis [9–15]. Chronic cough and sputum production are also seen in patients who smoke but do not have post-bronchodilator airflow limitation [16], in whom they are associated with worse outcomes compared with those without these symptoms [17].

Until recently, chronic cough and sputum production have been mainly associated with COPD. Less is known about the characteristics of patients with asthma with these symptoms. Mucus plugging has long been recognized as a feature associated with more severe eosinophilia [18,19], although this appears unrelated to greater frequency of chronic cough and sputum production [19]. Similarly, chronic cough in asthma has been associated with increased healthcare utilization [20] and accelerated lung function decline [21,22]. Submucosal gland hypertrophy is a pathophysiological feature of some asthma phenotypes [23,24], with observational studies identifying chronic mucus production in patients with asthma and no smoking history [25,26].

Persistent cough with sputum has been described as chronic bronchitis or chronic mucus hypersecretion [7,21,27]. However, these terms infer that symptoms are fixed and long-standing or that patients have excessive mucus production. We propose that the term "frequent productive cough" provides a more appropriate descriptor that is applicable across asthma and COPD, is clearly distinguished from the historical definition of chronic bronchitis, and advances the characterization of this clinical problem and potential for symptom variability across asthma and/or COPD without inferring a specific pathology.

Frequent productive cough can be assessed using the St George's Respiratory Questionnaire (SGRQ) [28], which asks patients about the frequency of cough and sputum (phlegm) production over the previous 3 months. The SGRQ criteria have been used previously when describing chronic mucus hypersecretion in patients with and without COPD [7] and chronic bronchitis in patients with COPD [12,27,29]. Notably, these studies did not include patients with asthma.

Here, we present our findings on frequent productive cough across a broad population of patients with asthma and/or COPD enrolled in NOVELTY (NOVEL observational longiTudinal studY; NCT02760329) [30], describing the relationship between frequent productive cough and disease characteristics, disease burden, and exacerbation risk.

2. Methods

2.1. NOVELTY study design

NOVELTY is a global, prospective, 3-year observational study of ~12,000 patients with a diagnosis or suspected diagnosis of asthma and/or COPD. The NOVELTY study design [30] and patient population [31] have been described previously. Patients were enrolled by primary care physicians, pulmonologists, or allergists from active clinical practices in 18 countries. To ensure sufficient representation of subgroups of interest, recruitment was stratified by physician-assigned diagnosis (asthma, asthma+COPD, or COPD) and by physician-assessed severity (mild, moderate, or severe); no diagnostic or severity criteria were prespecified to physicians to avoid prior assumptions about mechanisms and to allow generalizability of the findings to routine clinical practice. The NOVELTY study was approved in each participating country by the relevant institutional review boards and all patients provided written informed consent.

2.2. Frequent productive cough definition

Frequent productive cough was defined using two SGRQ items: "Over the past 3 months, I have coughed …" and "Over the past 3 months, I have brought up phlegm (sputum) …". Item responses ranged from 0 to 4 ("Not at all" – 0, "Only with chest infections" – 1, "A few days a month" – 2, "Several days a week" – 3, and "Most days a week" – 4). Patients were classified as having frequent productive cough if they answered "most days a week" or "several days a week," i.e., scored ≥3 on both items. Patients who scored ≤2 for either SGRQ item were classified as not having frequent productive cough.

Separately, to explore the spectrum of possible presentations, patients who scored ≥3 for only one of the SGRQ cough or sputum production items were classified as having frequent cough or frequent sputum production, respectively. Patients who scored ≥3 for the SGRQ cough item and ≤1 for the SGRQ sputum production item were classified as having frequent dry (non-productive) cough. Data for a third smaller

Table 1
Baseline patient demographics by physician-assessed diagnostic group and frequent productive cough status.

	Asthma (N = 3754)		Asthma+COPD (N = 887)		COPD (N = 2484)		Total (N = 7125)	
	With FPC	Without FPC	With FPC	Without FPC	With FPC	Without FPC	With FPC	Without FPC
FPC status, n (%)	939/3754 (25.0)	2815/3754 (75.0)	344/887 (38.8)	543/887 (61.2)	946/2484 (38.1)	1538/2484 (61.9)	2229/7125 (31.3)	4896/7125 (68.7)
Age, mean (SD), y	55.2 (15.8)	53.1 (15.9)	63.9 (10.2)	66.2 (9.5)	66.6 (9.7)	67.6 (9.0)	61.4 (13.8)	59.1 (15.2)
Sex								
Males, n/N1 (%)[a]	355/1376 (25.8)	1021/1376 (74.2)	190/497 (38.2)	307/497 (61.8)	593/1544 (38.4)	951/1544 (61.6)	1138/3417 (33.3)	2279/3417 (66.7)
Females, n/N1 (%)[a]	584/2378 (24.6)	1794/2378 (75.4)	154/390 (39.5)	236/390 (60.5)	353/940 (37.6)	587/940 (62.4)	1091/3708 (29.4)	2617/3708 (70.6)
Body mass index (kg/m^2)								
Patients with data available, n	862	2609	319	527	889	1444	2070	4580
Mean (SD)	28.7 (7.0)	27.7 (6.2)	28.8 (6.4)	28.0 (6.1)	27.1 (6.0)	27.7 (5.9)	28.0 (6.6)	27.7 (6.1)
Proportion of patients by region, n/N1 (%)[a]								
Australia	73/253 (28.9)	180/253 (71.1)	39/93 (41.9)	54/93 (58.1)	54/149 (36.2)	95/149 (63.8)	166/495 (33.5)	329/495 (66.5)
Canada	105/388 (27.1)	283/388 (72.9)	33/79 (41.8)	46/79 (58.2)	93/245 (38.0)	152/245 (62.0)	231/712 (32.4)	481/712 (67.6)
Europe	373/1566 (23.8)	1193/1566 (76.2)	163/429 (38.0)	266/429 (62.0)	447/1112 (40.2)	665/1112 (59.8)	983/3107 (31.6)	2124/3107 (68.4)
Japan	110/448 (24.6)	338/448 (75.4)	31/97 (32.0)	66/97 (68.0)	31/135 (23.0)	104/135 (77.0)	172/680 (25.3)	508/680 (74.7)
Korea	73/293 (24.9)	220/293 (75.1)	19/57 (33.3)	38/57 (66.7)	17/79 (21.5)	62/79 (78.5)	109/429 (25.4)	320/429 (74.6)
Latin America	83/339 (24.5)	256/339 (75.5)	10/33 (30.3)	23/33 (69.7)	132/405 (32.6)	273/405 (67.4)	225/777 (29.0)	552/777 (71.0)
USA	122/467 (26.1)	345/467 (73.9)	49/99 (49.5)	50/99 (50.5)	172/359 (47.9)	187/359 (52.1)	343/925 (37.1)	582/925 (62.9)
Proportion of patients by ethnicity, n/N1 (%)[a]								
Caucasian	669/2646 (25.3)	1977/2646 (74.7)	269/687 (39.2)	418/687 (60.8)	806/2058 (39.2)	1252/2058 (60.8)	1744/5391 (32.4)	3647/5391 (67.6)
African American	20/114 (17.5)	94/114 (82.5)	13/23 (56.5)	10/23 (43.5)	40/87 (46.0)	47/87 (54.0)	73/224 (32.6)	151/224 (67.4)
North East Asian[b]	182/740 (24.6)	558/740 (75.4)	45/146 (30.8)	101/146 (69.2)	46/204 (22.5)	158/204 (77.5)	273/1090 (25.0)	817/1090 (75.0)
South East Asian	17/66 (25.8)	49/66 (74.2)	7/12 (58.3)	5/12 (41.7)	4/15 (26.7)	11/15 (73.3)	28/93 (30.1)	65/93 (69.9)
Other	51/188 (27.1)	137/188 (72.9)	10/19 (52.6)	9/19 (47.4)	50/120 (41.7)	70/120 (58.3)	111/327 (33.9)	216/327 (66.1)
Proportion of patients by smoking status, n/N1 (%)[a]								
Current smoker	95/269 (35.3)	174/269 (64.7)	114/210 (54.3)	96/210 (45.7)	340/653 (52.1)	313/653 (47.9)	549/1132 (48.5)	583/1132 (51.5)
Former smoker	316/1191 (26.5)	875/1191 (73.5)	196/582 (33.7)	386/582 (66.3)	541/1672 (32.4)	1131/1672 (67.6)	1053/3445 (30.6)	2392/3445 (69.4)
Never smoker	528/2294 (23.0)	1766/2294 (77.0)	34/95 (35.8)	61/95 (64.2)	65/159 (40.9)	94/159 (59.1)	627/2548 (24.6)	1921/2548 (75.4)
Chronic bronchitis, n (%)	38 (4.0)	47 (1.7)	43 (12.5)	25 (4.6)	75 (7.9)	67 (4.4)	156 (7.0)	139 (2.8)
SGRQ total score								
Patients with data available, n	938	2807	344	542	939	1535	2221	4884
Mean (SD)	42.7 (21.2)	25.1 (18.8)	51.3 (21.8)	32.0 (18.7)	51.6 (20.5)	35.7 (20.0)	47.8 (21.4)	29.2 (19.8)

COPD, chronic obstructive pulmonary disease; FPC, frequent productive cough; N, total number of patients in the sample; n, number of patients meeting criteria; N1, number of patients with available data; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire.

FPC: experienced cough and brought up phlegm several or most days a week (SGRQ cough and sputum scores $\geq$3) in the past 3 months. Where no denominator is reported, N1 = N.

[a] Percentage values for the proportion of patients with and without FPC were calculated using the total number of patients with that demographic/clinical variable in each diagnostic and severity group as the denominator.

[b] Including Japanese patients.

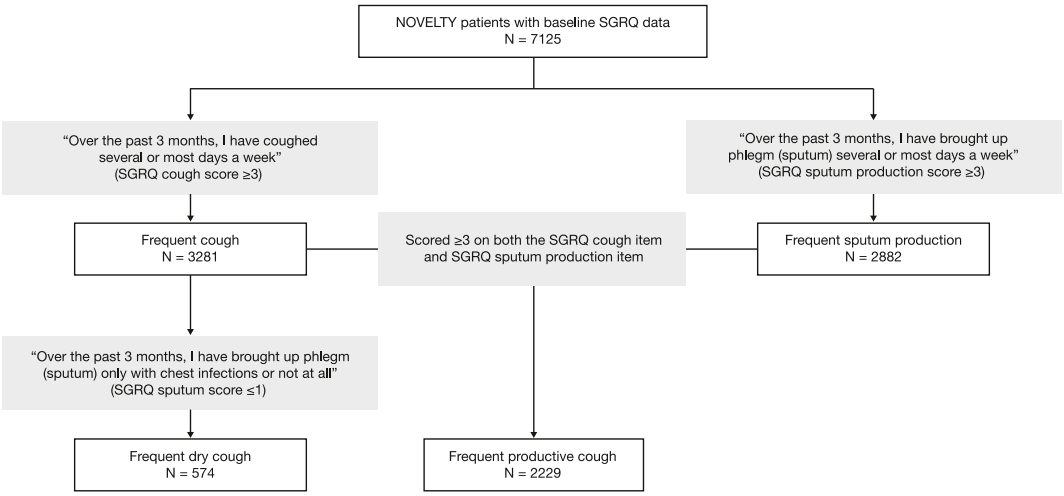


Fig. 1. Summary of NOVELTY patients included in the analysis by frequent cough and/or sputum production status.
Frequent cough and frequent sputum production were not mutually exclusive. N, number of patients. NOVELTY, NOVEL observational longiTudinal study; SGRQ, St George's Respiratory Questionnaire.

subset of patients with frequent cough who scored ≥3 for the SGRQ cough item and scored 2 for the SGRQ sputum production item are not reported.

2.3. Study assessments and outcomes

Data from the baseline and 1-year follow-up clinical study visits were used, as recorded by physicians in electronic case report forms and from patient-reported outcomes completed at baseline. The prevalence of frequent productive cough was evaluated relative to baseline disease characteristics, including physician-assigned diagnosis, physician-assessed severity, comorbidities, medications, biomarkers, spirometry, exacerbation history, patient-reported outcome questionnaires, and exposure history.

Exposure history included ever being exposed to pollutants at home/work and occupational exposure to dust/fumes. Comorbidities were recorded by the physician at baseline. Bronchiectasis was derived from physician diagnosis and/or a record of abnormal computed tomography findings. Allergic rhinosinusitis was defined as allergic, seasonal or perennial rhinitis/sinusitis. Medications were analyzed by class. Biomarkers included blood neutrophil and eosinophil counts from consenting patients and fractional exhaled nitric oxide, as measured per American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations [32]. Spirometry measures included bronchodilator responsiveness, post-bronchodilator forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and FEV_1/FVC ratio. Predicted and lower limit of normal (LLN) values were based on Global Lung Function Initiative multiethnic reference equations [33]. Physician-reported exacerbations were defined based on ATS/ERS recommendations for asthma [34] and consensus recommendations for COPD [35] as events "beyond the patient's usual day-to-day variance".

Baseline patient-reported questionnaires including the SGRQ were undertaken either in person at baseline visit or remotely, via a web-based application or telephone. These included a question on self-reported episodes of symptomatic worsening in the previous 3 months, with patients asked: "During the past 3 months, how many times has your breathing worsened beyond what you usually experience in a typical day (e.g., increased shortness of breath, wheezing, cough, or chest tightness)?". Response options ranged numerically from "none" to "12+". This question was separate from how these symptoms were otherwise recorded. Questionnaires were completed at baseline by approximately 60% of patients.

To assess the relationship between frequent productive cough at baseline and risk of exacerbations in the subsequent 12 months, outcomes recorded at 1 year included all physician-reported exacerbations during the previous 12 months; exacerbations were further categorized by type of management as those treated with oral corticosteroids (OCS), antibiotics, emergency room/department visit, or resulting in hospital admission.

2.4. Statistical analysis

All patients with complete baseline data for both SGRQ items used to define frequent productive cough were included in the analysis, with results presented for the overall cohort and stratified by physician-assigned diagnosis and physician-assessed severity. Descriptive analyses for the baseline distributions of frequent productive cough, frequent cough, frequent sputum production, and frequent dry cough were performed. Demographics and disease characteristics for patients with versus without frequent productive cough were compared, as were the demographics for patients included versus excluded (due to insufficient baseline SGRQ data) from the analysis.

Associations between frequent productive cough and baseline patient demographic and disease characteristics were assessed within each asthma and/or COPD diagnostic group using multivariate logistic regression, with frequent productive cough as the outcome. Covariates were kept to a minimum to avoid over-adjustment; age, sex, and current smoking status were selected using a directed acyclic graph. Associations with post-bronchodilator FEV_1 were assessed per 10% decrement.

The associations between frequent productive cough and exacerbations and exacerbation-related healthcare utilization at 1-year were estimated for each diagnostic label. Associations were assessed using multivariate logistic regression, with odds ratios (ORs) and corresponding 95% confidence intervals (CIs) presented. Exacerbation outcomes were the response variables and frequent productive cough the explanatory variable. Again, age, sex, and current smoking status were selected as covariates.

No adjustment was made for multiple testing. Statistical analysis was performed in Rstudio (R version 3.6.1, Rstudio version 1.2.1086).

3. Results

Overall, 7125 patients with complete SGRQ data were included. Of these, 3754 (52.7%) had asthma, 887 (12.4%) had asthma+COPD, and 2484 (34.9%) had COPD diagnoses. Severity distribution varied considerably among diagnostic groups (Supplementary Table 1). Supplementary Table 2 presents demographics of patients included and excluded (due to lack of SGRQ data) from this analysis. Smoking

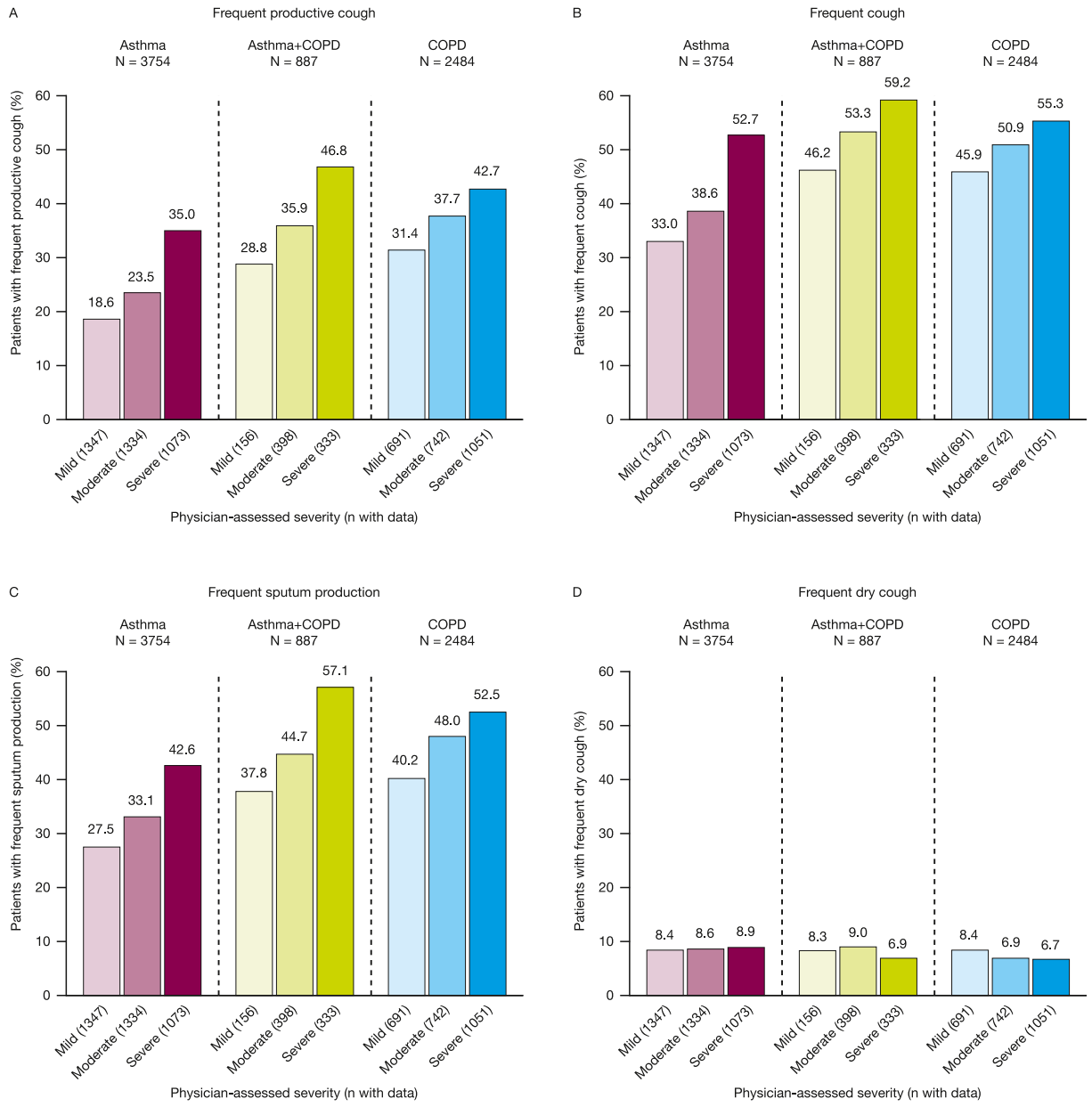


Fig. 2. Distribution of patients with (*A*) frequent productive cough, (*B*) frequent cough, (*C*) frequent sputum production, and (*D*) frequent dry cough across physician-assigned diagnostic and severity groups.
See Fig. 1 for classification. Frequent productive cough: cough and sputum production several or most days a week (SGRQ cough and sputum scores ≥3) in the past 3 months. Frequent cough: cough several or most days a week (SGRQ cough score ≥3) in the past 3 months. Frequent sputum production: sputum production several or most days a week (SGRQ sputum scores ≥3) in the past 3 months. Frequent dry (non-productive) cough: cough several or most days a week (SGRQ cough score ≥3) and sputum production only with chest infection or not at all (SGRQ sputum production score ≤1) in the past 3 months. COPD, chronic obstructive pulmonary disease; N, total number of patients in the sample; n, number of patients with data; SGRQ, St George's Respiratory Questionnaire.

prevalence varied by region, with the proportion of current smokers ranging from 8.8% in Japan to 23.7% in the USA.

3.1. Distribution of cough types

Frequent productive cough was reported by 31.3% of patients (2229/7125) (Table 1 and Fig. 1); separately, frequent cough was identified in 46.0% of patients (3281/7125), frequent sputum production in 40.4% (2882/7125), and frequent dry cough in 8.1% (574/7125). Frequent cough and/or frequent sputum production were identified in 55.2% of patients (3934/7125) (Supplementary Fig. 1).

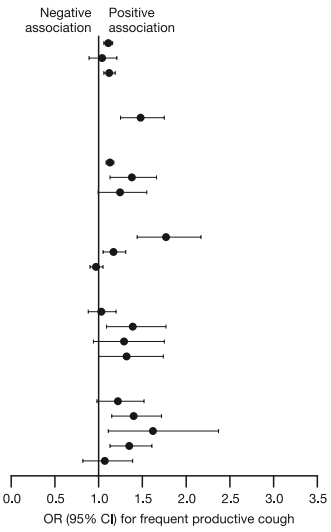
Frequent productive cough was common across all diagnoses but was more common among patients with asthma+COPD (38.8%) and COPD (38.1%) than asthma (25.0%) (Table 1 and Supplementary Fig. 2). A similar pattern was observed for frequent cough and frequent sputum production but not for frequent dry cough (Supplementary Fig. 2). Generally, the proportion of patients with each type of frequent cough and/or sputum production increased with greater physician-assessed disease severity across diagnostic groups (Fig. 2A–C), comprising over one-third of patients with severe asthma and over 40% of patients with severe COPD; this pattern was not observed for frequent dry cough, which was less common with increasing severity of COPD (Fig. 2D).

3.2. Baseline characteristics of frequent productive cough

Baseline demographics for patients with and without frequent

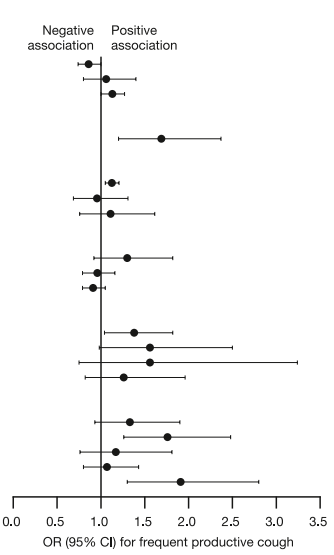
A

Variable	n with data	Frequency (%) or mean [SD]	OR	95% CI
Demographics				
Age (per +10 y)	3754	53.6 [15.9]	1.11	[1.06–1.16]
Men vs women	3754	1376 (36.7)	1.04	[0.89–1.21]
BMI (per +5 kg/m²)	3471	27.9 [6.4]	1.12	[1.06–1.19]
Exposure history				
Pollutants at home/work*, yes versus no	3738	2546 (68.1)	1.48	[1.25–1.75]
Lung function				
Post-FEV_1, % predicted (per -10%)	3068	86.5 [20.3]	1.12	[1.08–1.17]
Post-FEV_1/FVC < LLN, yes versus no	3077	722 (23.5)	1.37	[1.13–1.65]
Bronchodilator responsiveness†, yes versus no	3039	463 (15.2)	1.24	[0.99–1.54]
Biomarkers				
Blood neutrophils (per 10^9/L)‡	1779	4.4 [1.7]	1.77	[1.44–2.17]
Blood eosinophils (per 10^9/L)‡	1764	0.21 [0.14]	1.17	[1.05–1.31]
FeNO (per ppb)‡,§	3290	29.7 [23.8]	0.97	[0.90–1.05]
Respiratory comorbidities				
Allergic rhinosinusitis‖, yes versus no	3754	2236 (59.6)	1.03	[0.88–1.20]
Non-allergic rhinosinusitis, yes versus no	3754	349 (9.3)	1.39	[1.09–1.77]
Nasal/sinus polyps, yes versus no	3754	207 (5.5)	1.29	[0.94–1.75]
Sleep apnea, yes versus no	3754	262 (7.0)	1.32	[1.00–1.74]
Non-respiratory comorbidities				
Depression/anxiety, yes versus no	3754	454 (12.1)	1.22	[0.98–1.52]
GERD, yes versus no	3754	540 (14.4)	1.40	[1.15–1.72]
CHD or heart failure, yes versus no	3754	124 (3.3)	1.62	[1.11–2.37]
Hypertension, yes versus no	3754	975 (26.0)	1.35	[1.13–1.61]
Osteoarthritis, yes versus no	3754	314 (8.4)	1.07	[0.82–1.39]



B

Variable	n with data	Frequency (%) or mean [SD]	OR	95% CI
Demographics				
Age (per +10 y)	887	65.3 [9.9]	0.86	[0.74–1.00]
Men vs women	887	497 (56.0)	1.06	[0.80–1.40]
BMI (per +5 kg/m²)	846	28.3 [6.2]	1.13	[1.00–1.27]
Exposure history				
Pollutants at home/work*, yes versus no	886	674 (76.1)	1.69	[1.20–2.37]
Lung function				
Post-FEV_1, % predicted (per -10%)	741	68.5 [22.0]	1.13	[1.05–1.21]
Post-FEV_1/FVC < LLN, yes versus no	740	475 (64.2)	0.96	[0.70–1.31]
Bronchodilator responsiveness†, yes versus no	731	152 (20.8)	1.11	[0.77–1.61]
Biomarkers				
Blood neutrophils (per 10^9/L)‡	511	4.9 [1.9]	1.30	[0.92–1.82]
Blood eosinophils (per 10^9/L)‡	505	0.20 [0.14]	0.96	[0.79–1.16]
FeNO (per ppb)‡,§	782	23.6 [19.7]	0.91	[0.79–1.05]
Respiratory comorbidities				
Allergic rhinosinusitis‖, yes versus no	887	383 (43.2)	1.38	[1.04–1.82]
Non-allergic rhinosinusitis, yes versus no	887	80 (9.0)	1.56	[0.98–2.50]
Nasal/sinus polyps, yes versus no	887	31 (3.5)	1.56	[0.75–3.24]
Sleep apnea, yes versus no	887	96 (10.8)	1.26	[0.82–1.96]
Non-respiratory comorbidities				
Depression/anxiety, yes versus no	887	167 (18.8)	1.33	[0.93–1.90]
GERD, yes versus no	887	177 (20.0)	1.76	[1.26–2.48]
CHD or heart failure, yes versus no	887	103 (11.6)	1.17	[0.76–1.81]
Hypertension, yes versus no	887	346 (39.0)	1.07	[0.80–1.43]
Osteoarthritis, yes versus no	887	137 (15.4)	1.91	[1.30–2.80]



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Variable	n with data	Frequency (%) or mean [SD]	OR	95% CI
Demographics				
Age (per +10 y)	2484	67.2 [9.3]	0.98	[0.89–1.07]
Men vs women	2484	1544 (62.2)	1.10	[0.93–1.31]
BMI (per +5 kg/m²)	2333	27.5 [6.0]	0.94	[0.87–1.01]
Exposure history				
Pollutants at home/work*, yes versus no	2475	1926 (77.8)	1.35	[1.10–1.66]
Lung function				
Post-FEV_1, % predicted (per -10%)	2090	60.9 [23.2]	1.13	[1.08–1.17]
Post-FEV_1/FVC < LLN, yes versus no	2089	1380 (66.1)	1.44	[1.19–1.75]
Bronchodilator responsiveness†, yes versus no	2021	256 (12.7)	1.00	[0.76–1.32]
Biomarkers				
Blood neutrophils (per 10^9/L)‡	1292	5.0 [1.7]	1.67	[1.32–2.11]
Blood eosinophils (per 10^9/L)‡	1298	0.18 [0.11]	1.19	[1.04–1.35]
FeNO (per ppb)‡,§	2083	19.6 [15.5]	0.88	[0.80–0.97]
Respiratory comorbidities				
Allergic rhinosinusitis‖, yes versus no	2484	381 (15.3)	1.40	[1.11–1.75]
Non-allergic rhinosinusitis, yes versus no	2484	64 (2.6)	1.29	[0.77–2.14]
Nasal/sinus polyps, yes versus no	2484	24 (1.0)	2.22	[0.97–5.09]
Sleep apnea, yes versus no	2484	258 (10.4)	1.01	[0.77–1.32]
Non-respiratory comorbidities				
Depression/anxiety, yes versus no	2484	368 (14.8)	1.18	[0.94–1.49]
GERD, yes versus no	2484	361 (14.5)	0.90	[0.71–1.13]
CHD or heart failure, yes versus no	2484	390 (15.7)	1.28	[1.02–1.60]
Hypertension, yes versus no	2484	1121 (45.1)	0.89	[0.76–1.06]
Osteoarthritis, yes versus no	2484	280 (11.3)	1.25	[0.96–1.62]

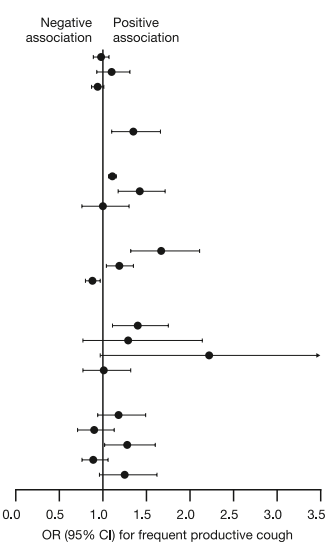

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Fig. 3. Association between baseline variables and frequent productive cough by physician-assigned diagnosis of (*A*) asthma, (*B*) asthma+COPD, and (*C*) COPD. Multivariate regression analysis adjusted for age, sex, and current smoking status; for "*yes versus no*," no means "no or missing." ATS, American Thoracic Society; BMI, body mass index; CAPTURE, COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk; CHD, coronary heart disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ERS, European Respiratory Society; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; LLN, lower limit of normal; n, number of patients with data; OR, odds ratio; ppb, parts per billion; SD, standard deviation. *Pollutants at home/work was derived from question 1 from the CAPTURE questionnaire [36]: "Have you ever lived or worked in a place with dirty or polluted air, smoke, second-hand smoke, or dust?" †Bronchodilator responsiveness was defined as ≥12% and 200 mL increase in FEV_1. ‡Per doubling. §FeNO was unadjusted for smoking status and was measured per ATS/ERS recommendations [32]. ||Allergic rhinosinusitis was defined as allergic, seasonal or perennial rhinitis/sinusitis.

productive cough are reported by diagnostic and diagnostic/severity groups (Table 1 and Supplementary Table 1). Distribution of frequent productive cough by region varied considerably in the asthma+COPD and COPD groups, but less so for asthma; the highest and lowest prevalence of frequent productive cough were seen in the USA (37.1%) and Japan (25.3%), respectively. Overall, frequent productive cough prevalence was higher in current smokers (48.5%) than former/never smokers (30.6% and 24.6%, respectively), but it was more common among non-smokers with COPD (40.9%) than non-smokers with asthma (23.0%).

Among included patients, physicians recorded chronic bronchitis and bronchiectasis diagnoses in 4.1% and 5.9%, respectively; for both conditions, the highest proportion of patients was observed in the asthma+COPD group, and the lowest proportion in the asthma group. Both conditions were more common in patients with versus without frequent productive cough, although only 44.6% of patients (187/419) with bronchiectasis reported frequent productive cough symptoms (Table 1 and Supplementary Table 3).

At baseline, more patients with frequent productive cough, compared to those without it, were receiving triple therapy (inhaled corticosteroids, long-acting β_2-agonists, and long-acting muscarinic antagonists) across all diagnostic groups (Supplementary Table 3). A small number of patients were taking targeted medications for chronic cough and sputum production such as roflumilast, chronic antibiotics or mucolytics.

More patients with versus without frequent productive cough experienced exacerbations in the 12 months prior to baseline, and patient-reported episodes of symptomatic worsening in the 3 months prior to baseline, in all diagnostic groups (Supplementary Table 3) and across disease severity (Supplementary Tables 4–6). SGRQ-assessed health status was substantially worse in patients with frequent productive cough in all diagnostic groups (Table 1).

3.3. Factors associated with frequent productive cough

Associations between baseline demographic and disease variables and frequent productive cough are presented in Fig. 3. Across all diagnostic groups, frequent productive cough was independently associated with ever being exposed to pollutants at work/home (OR 1.50 [95% CI 1.33–1.69]) and with reduced post-bronchodilator FEV_1 (OR per 10% decrement 1.14 [95% CI 1.11–1.16]). Among patients with asthma or COPD, frequent productive cough was associated with persistent airway obstruction ($FEV_1/FVC < LLN$). Patients with asthma or COPD and frequent productive cough, but not those with asthma+COPD, had higher blood neutrophil and eosinophil counts than those without frequent productive cough. Allergic rhinosinusitis was associated with frequent productive cough in patients with asthma+COPD or COPD, whereas non-allergic rhinosinusitis was associated with frequent productive cough in patients with asthma. Increased frequency of other comorbidities among patients with frequent productive cough varied across diagnostic groups; those with asthma or asthma+COPD were more likely to have gastroesophageal reflux disease (GERD) and those with asthma only or COPD only were more likely to have coronary heart disease or heart failure.

3.4. Frequent productive cough association with exacerbations

Overall and across diagnoses, having frequent productive cough at baseline was associated with an increased risk of ≥1 exacerbation over the subsequent 12 months (OR 1.71 [95% CI 1.52–1.93]), including those resulting in hospital admission (OR 1.93 [95% CI 1.50–2.48]) (Fig. 4 and Supplementary Fig. 3). This pattern was also observed for categories of exacerbations treated with OCS (OR 1.87 [1.63–2.14]) and with antibiotics (OR 1.86 [1.62–2.14]).

4. Discussion

In our analysis of a large global observational cohort of >7000 real-world patients with a diagnosis of asthma and/or COPD, we have established the concept of "frequent productive cough" as a common clinical trait associated with worse clinical and patient-reported disease and poorer clinical outcomes across asthma and/or COPD. Specifically, our results revealed that nearly one-third of patients with SGRQ data available in this NOVELTY sub-cohort reported symptoms at baseline consistent with frequent productive cough. Frequent productive cough was less common in patients with asthma compared with asthma+COPD and COPD; despite this, frequent productive cough represented a more common clinical presentation than frequent dry cough in patients with asthma (25.0% vs 8.6%). Frequent productive cough was present across all categories of physician-assessed severity, including patients characterized as having mild disease and patients with a diagnosis of COPD but without post-bronchodilator airflow obstruction on spirometry assessment.

Patients with asthma and/or COPD and frequent productive cough at baseline were at a greater risk of experiencing exacerbations over the subsequent 12 months compared with those without it, even when adjusted for smoking status. This corroborates previous findings of a link between cough and sputum production symptoms and exacerbation risk [7,10–12,37]. Frequent productive cough at baseline was also associated with an increased use of exacerbation-related healthcare resources, as previously reported in patients with COPD and similar symptoms [10]. At baseline, a higher proportion of patients with frequent productive cough had a history of exacerbations in the previous 12 months, as seen previously when using these SGRQ items to assess symptoms described as chronic bronchitis [7,12].

As expected, given the established relationship between smoking and historically-defined chronic bronchitis [11,14,38], a higher proportion of current smokers had frequent productive cough than former and non-smokers. As with previous SGRQ-based studies of symptoms characteristic of frequent productive cough [7,12,29], a higher proportion of patients with versus without frequent productive cough were current smokers. However, this relationship may be confounded by patients with more severe disease being more likely to quit smoking [31]. Furthermore, when patients stop smoking and ciliary function returns, there can be a period of increased coughing [39].

Varying prevalence of frequent productive cough was observed across regions, ranging from 25% of patients in Japan to 37% of patients in the USA. One potential reason for this variance may be differences in smoking prevalence in each region, with current smoking rates ranging from 9% in Japan to almost a quarter of patients in the USA, which could be an interesting topic for future publication. Underlying differences in

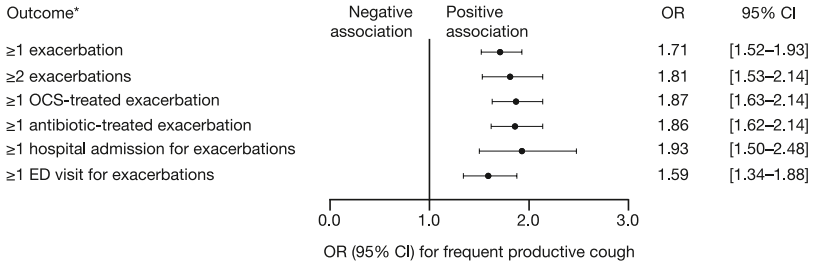

Fig. 4. Associations between frequent productive cough at baseline and physician-reported exacerbations and related outcomes over the subsequent year, reported at year 1 visit in the overall patient population (N = 5710).
Multivariate regression analyses adjusted for age, sex, and current smoking status; patients with bronchiectasis were removed from this analysis. ATS, American Thoracic Society; CI, confidence interval; ED, emergency department; ERS, European Respiratory Society; OCS, oral corticosteroid; OR, odds ratio. *Exacerbations were defined based on ATS/ERS recommendations as beyond the patient's usual day-to-day variance [34].

the populations recruited and the diagnostic criteria used by physicians in the NOVELTY study in each region could also account for some variance. Furthermore, a diagnosis of GERD was reported at a low frequency in NOVELTY when compared with other large studies such as COPDGene [12], although this is often under-diagnosed. Nevertheless, frequent productive cough was present in patients from all regions analyzed, suggesting a need to better target this global clinical trait in obstructive lung disease.

Corroborating previous findings in patients with symptoms characteristic of frequent productive cough, patients in NOVELTY with versus without frequent productive cough were more likely to have greater airflow limitation [7,12] and cardiovascular disease [40]. Although GERD was associated with cough and sputum production symptoms in patients with asthma or asthma+COPD, this was not the case for patients with COPD, which contrasts with findings by the COPDGene study [12,27]. This may be explained by differences in the patient populations and diagnostic practices, with NOVELTY including patients from regions outside of the USA. Furthermore, unlike many large COPD studies, such as COPDGene, NOVELTY includes a population of never-smokers who were not represented in the COPDGene findings. In asthma, frequent productive cough was associated with non-allergic rhinosinusitis, but not allergic rhinosinusitis, whereas for COPD the opposite was observed. Previous observational study findings on frequent productive cough symptoms in asthma have suggested an association with allergic rhinosinusitis [41], but we were unable to corroborate this within a larger real-world asthma population.

Current drugs and treatment strategies for patients with asthma and/or COPD may have only limited effects on frequent productive cough symptoms, supporting the need to identify specific underlying mechanisms and develop novel therapeutic approaches targeting these symptoms [42]. Randomized clinical trials of azithromycin and aclidinium bromide enrolled patients with COPD and frequent productive cough [43,44], while multiple clinical studies are underway to investigate "chronic cough". This, like frequent productive cough, was common across patients with asthma and/or COPD in the NOVELTY cohort. However, many studies of chronic cough do not include any analysis of patients with frequent productive cough and indeed some actively exclude patients with chronic bronchitis [45,46]. In addition, multiple studies of refractory chronic cough exclude patients with FEV_1/FVC <60% [47–51], which results in many patients with COPD being ineligible. This is despite recent clinical guidelines for chronic cough calling for more investigation into the trait [52,53].

As demonstrated in our findings, frequent productive cough was present in patients with asthma and/or COPD in all physician-assessed severity categories and was an indicator of adverse clinical outcomes in these groups. This suggests a need for existing chronic cough clinical trials to include subgroup analysis of patients with versus without frequent productive cough, and for the design of clinical trials of new and existing therapies which specifically target the frequent productive cough trait. In addition, few studies examine cough outside of the context of obstructive lung disease, and the differences between the pathophysiology of respiratory disease and chronic cough are poorly understood.

In terms of the patient populations included in frequent productive cough trials, there is a significant need for studies to include broader patient populations that are more representative of the real world. This in turn will aid in the identification of traits which may be targeted to improve diagnosis, and ultimately treatment. Several groups have previously been identified as requiring greater representation in treatment clinical trials to facilitate understanding of COPD disease trajectory, including patients with COPD aged <50 years and patients with pre-COPD [54].

Chronic bronchitis has been described as a "treatable trait," with proposed therapies including carbocisteine, long-term low-dose macrolides, and roflumilast [55]. Only a small proportion of patients in our analysis were receiving these medications, and from cross-sectional analysis, their effects on frequent productive cough could not be determined. Of note, these therapies are generally recommended in more severe patient populations [2,56], whereas frequent productive cough was present at all physician-assessed severity levels. Further, the symptoms described here as frequent productive cough may have heterogeneous underlying pathophysiology, including bronchiectasis and increased mucus production, which would influence treatment approaches. Future analysis of stored biosamples in NOVELTY may allow identification of genetic markers of frequent productive cough, such as variations in MUC5AC and MUC5B [57].

In contrast to the frequent productive cough findings, the proportion of patients with frequent dry cough was similar across diagnostic groups, with no clear pattern observed across severity categories. This suggests that different mechanisms may be involved, with further research needed to investigate the pathobiology of these two clinically heterogeneous traits.

A strength of this analysis is its use of the previously established SGRQ-based definition of chronic bronchitis-like symptoms [27], which requires a much shorter (3-month) period than the 2 years needed for the historical chronic bronchitis definition. Further, this SGRQ-based definition has previously been shown to better predict COPD exacerbations than historically defined chronic bronchitis [12]. Patient-reported outcome instruments like the SGRQ [28] can be useful in research settings and, to some extent, clinical practice, where the presence and severity of patient-reported symptoms are important when identifying and diagnosing patients with obstructive lung disease [2,56]. The SGRQ is already extensively used in respiratory research; therefore, the presence of frequent productive cough could be used to identify patients at risk of poorer outcomes. Our findings should prompt analysis of data from existing and future randomized clinical trials assessing pharmacologic treatment options for asthma and/or COPD that use the SGRQ to further explore the utility of the frequent productive cough questions for patient stratification and its relationship with clinically relevant outcomes.

Furthermore, this analysis benefits from the inclusion of patients across all physician-assessed severity levels, multiple countries, and several ethnicities. Previous analyses have assessed various definitions of chronic bronchitis in asthma [21,41], COPD [7,11,12,29,58], or the general population [8,59,60] but not across the obstructive lung disease spectrum, even though chronic cough and sputum production occur frequently in both asthma and COPD [2,41,56]. The inclusion of patients with asthma and/or COPD provides evidence to support further research into frequent productive cough as a phenotype of obstructive lung disease and its association with worse outcomes in these diagnoses. This may support the development of targeted therapies for frequent productive cough, as opposed to treatments guided by diagnostic label only.

Since the prevalence of symptoms characteristic of frequent productive cough seems to increase with age [11,41], data comparisons between physician-assigned diagnostic groups may be hindered by differences in mean patient age. Curiously, some patients reported frequent sputum production without frequent cough; one possible explanation is that they were referring to the clearing of mucus originating from nasal secretions (previously "post-nasal drip," now termed "upper airway cough syndrome" [61]), but this remains unclear. This analysis did not include any imaging data, limiting the diagnosis of bronchiectasis and preventing the possibility of examining the relationship between these symptoms and mucus plugging, as investigated recently [62]. Analysis of sputum was not possible due to the size and scope of the study.

5. Conclusion

Frequent productive cough, as self-reported with the SGRQ, represents an important clinical trait that is common across the spectrum of obstructive lung disease. Although asthma and COPD are sometimes simplistically characterized by wheeze and cough, respectively, this analysis confirms that both cough and sputum production are frequent chronic symptoms in patients with asthma and/or COPD. Frequent productive cough was present across all physician-assessed severity levels, was associated with significant disease burden, and was an important indicator of the risk of adverse clinical outcomes. Efforts to reduce frequent cough and sputum production symptoms may, therefore, be an important component of the management strategy for these patients. Further research is required to understand the different pathobiologies underlying frequent productive cough and support the development of targeted therapies that improve patient outcomes rather than conventional treatment strategies based on either diagnostic label or clinical trait alone. Clinical trials investigating frequent productive cough should be designed to include broader populations to ensure that new therapies effectively target this trait.

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

CRediT authorship contribution statement

Rod Hughes: Conceptualization, Methodology, Writing – original draft, Supervision, Writing – review & editing. **Eleni Rapsomaniki:** Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Christer Janson:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Christina Keen:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Barry J. Make:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Pierre-Régis Burgel:** Investigation, Writing – original draft, Writing – review & editing. **Erin L. Tomaszewski:** Methodology, Writing – original draft, Supervision, Writing – review & editing. **Hana Müllerová:** Conceptualization, Methodology, Writing – original draft, Supervision, Writing – review & editing. **Helen K. Reddel:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing.

Declaration of competing interest

R.H., E.R., C.K., E.L.T., and H.M. are employees of AstraZeneca; C.J. has received personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, and Orion; B.J.M. has received CME personal fees from American College of Chest Physicians, Eastern Pulmonary Society, Integritas Communications, Medscape, National Jewish Health, Novartis, Mt Sinai, Projects in Knowledge, WebMD, and Wolters Kluwer Health; medical advisory board fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Mylan, Novartis, Phillips, Third Pole, and Verona; personal fees for data safety and monitoring board from Quintiles and Spiration; grants from American Lung Association, AstraZeneca, GlaxoSmithKline; personal fees from AstraZeneca, GlaxoSmithKline, Optimum Patient Care Global Limited, Spiration, and Third Pole; funding from the NHLBI for the COPDGene study; P-R.B. has received personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Insmed, Pfizer, Vertex Pharmaceuticals, and Zambon; grants from Boehringer Ingelheim, GlaxoSmithKline and Vertex Pharmaceuticals; H.K.R. has participated in advisory boards for AstraZeneca, Chiesi, GlaxoSmithKline, Novartis, and Sanofi-Genzyme; and has received honoraria from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Sanofi, and Teva Pharmaceuticals for independent medical educational presentations; and independent research funding from AstraZeneca, GlaxoSmithKline and Novartis.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2022.106921.

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