Upper airway symptoms associate with the eosinophilic phenotype of COPD

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Shareable abstract (@ERSpublications)
Upper airway symptoms are common in COPD, and are associated with elevated CAT scores and more pronounced systemic and airway eosinophilia https://bit.ly/3iIKBUS

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Abstract

Background There is growing evidence that upper airway symptoms coexist with lower airway symptoms in COPD. Still, the prevalence and impact of upper airway disease on the nature and course of COPD remain unclear. We aimed to describe this in a cross-sectional study.

Methods We examined a cohort of COPD patients with pulmonary function tests, induced sputum, blood eosinophils, atopy tests and computed tomography (CT) of the paranasal sinuses. Lower airway symptoms were assessed using the COPD Assessment Test (CAT), and upper airway symptoms were assessed using the nasal subdomain of the 22-item Sino Nasal Outcome Test ($SNOT22_{nasal}$). We recruited patients from five sites in Denmark and Sweden. We excluded patients with a history of asthma.

Findings In total, 180 patients (female 55%, age 67±8 years, forced expiratory volume in 1 s (FEV_1 %) 52.4±16.6, Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage: A: 18%, B: 54%, C: 3%, D: 25%) were included in the study. Seventy-four patients (41%) reported high upper airway symptoms (UAS, defined as $SNOT22_{nasal} \geqslant 6$) with a median score of 10 (IQR 8–13). Patients with high UAS reported higher CAT scores (17.4±7.5 *versus* 14.9±6.6, $p<0.05$) and displayed higher fractions of eosinophils in blood (median 3.0% (IQR 1.6–4.2%) *versus* 2.3% (IQR 1.4–3.1%), $p<0.05$) and in induced sputum (median 1.8% (IQR 0.3–7.1%) *versus* median 0.5% (IQR 0–1.7%), $p<0.05$). No differences in atopy, CT findings or exacerbation rates were observed.

Conclusion COPD patients with upper airway disease showed increased evidence of eosinophilic disease and increased lower airway symptom burden.

Introduction

COPD has historically been viewed as a disease of the lower airways since its dominant features are chronic bronchitis, emphysema and irreversible airway obstruction [1]. Clinical phenotyping of COPD patients according to specific and treatable traits is a growing clinical and research area aiming at reducing overall disease burden, understanding underlying disease mechanisms and developing novel treatments targeting these mechanisms [2]. Several treatable traits have been identified, including coexisting cachexia, anxiety, hyperinflation and the eosinophilic phenotype. Addressing these traits alleviates the overall disease burden [2, 3, 4].

Coexisting upper airways symptoms (UAS) in COPD was acknowledged 20 years ago and confirmed in later observational studies [5–7]. Pan-airway inflammation has been reported in stable COPD and during acute exacerbations of COPD, as has the tendency of a correlation between UAS and COPD severity as well as a correlation between reduced nasal patency and the degree of airway obstruction [6, 8, 9]. However, studies in this field tend to be small and single-centre based, with important between-study definitions of UAS.

With this study, we aimed at reporting the prevalence of upper airway symptoms in a multicentre prospective observational study from clinics in both Denmark and Sweden, using a validated questionnaire and a pre-defined battery of diagnostic workup. We hypothesise that upper airway symptoms in COPD are a treatable trait associated with increased symptoms burden.

Methods

This study is a sub-study of a larger cross-sectional study, "BREATHE" [10], conducted between February 2017 and February 2019. Ethical approval was granted by the local ethics committees in Denmark and Sweden (H-16047428, SJ-668, DNR 2016/1069) and by the Danish Data Protection Agency.

We recruited patients from three specialist centres at Næstved Hospital and Bispebjerg University Hospital, University of Copenhagen, in Denmark and Skåne University Hospital, Lund University, in Sweden as well as two primary care centres (in Næset and Næsby) in Sweden. Patients seen in the outpatient clinics were a combination of newly referred for evaluation for respiratory disease and patients attending regular follow-up visits.

To be included in this study, patients needed to fulfil the following inclusion criteria: age⩾40 years, a history of smoking ⩾10 pack-years of tobacco and a post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) index <0.70.

Exclusion criteria were self-reported or physician-diagnosed asthma. Reversibility for β2-agonist was accepted unless it exceeded 400 mL and 15% from baseline FEV_1 in the absence of clinical suspicion of asthma [11]. We defined a suspicion of asthma as early onset of symptoms (before the age of 40) or a history of persistent respiratory symptoms in childhood or adolescence.

Medical history

Patients were interviewed by one of five trained medical doctors, and a focused medical history was obtained. Medical history included information on upper and lower airway symptoms, history of exacerbations, hospital or emergency department admissions, current or prior history of asthma, and other comorbidities such as heart disease, and current medication use.

Smoking history was quantified using pack-years of tobacco. One pack-year equals a consumption of 20 cigarettes daily for 1 year.

Exacerbations of COPD (AECOPD) were defined as self-reported worsening of respiratory symptoms requiring additional treatment with oral antibiotics and/or corticosteroids or admission to hospital equivalent to moderate and severe COPD exacerbations. Only patient-reported exacerbations were registered.

Questionnaires

All patients completed the following questionnaires on airway symptoms:

- The COPD Assessment Test (CAT) is an eight-item questionnaire validated to assess COPD symptom burden: "cough", "phlegm", "chest tightness", "dyspnoea", "limitations in physical activities", "confidence as well as sleep" and "overall daily energy levels" [12]. Patients score each item on a Likert scale from 0 ("I never cough") to 5 ("I cough all the time") with a maximum score of 40 points and a minimal clinically important difference (MCID) of 2 points [13].
- The 22-item Sino Nasal Outcome Test (SNOT22) assesses a wide range of symptoms from nasal symptoms, facial and ear pain, and more general symptoms such as fatigue and sleep disturbances [14]. Each item is scored on a Likert scale from 0 ("no problem") to 5 ("problem as bad as it can be"). The maximum score is 110, with an MCID of 9 points [15].
- The SNOT22 nasal subdomain ($SNOT22_{nasal}$) consists of seven items (no. 1–5+7–8) with a maximum score of 35 points: "need to blow nose", "sneezing", "runny nose", "nasal obstruction", "loss of smell or taste", "post-nasal discharge" and "thick nasal discharge". A cut-off for normality (or MCID) is not validated, but one study found a median overall SNOT22 score of 7 points in healthy volunteers [16]. Other subdomains include "Sleep", "otologic/facial" and "emotional" [17].

Definition of high UAS

We defined high upper airway symptoms as $SNOT22_{nasal}$⩾6. We chose this cut-off value as a score of 6 implies having either mild symptoms in almost all items or moderate–severe symptoms in one or two items.

Objective tests

Pulmonary function tests

Spirometry and bronchodilator responsiveness tests for β2-agonist were performed according to European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines using a Jaeger Spirometer (Intramedic®, Gentofte, Denmark) for recording FEV_1, FVC and FEV_1/FVC index [18].

Patients from the specialist centres (Næstved, Bispebjerg and Lund, n=151) underwent body plethysmography using a Jaeger Box (Intramedic®, Gentofte, Denmark) to obtain static lung volumes with single-breath carbon monoxide uptake measurements [19], but this test was not available at the primary care centres.

Induced sputum

We obtained induced sputum from the lower airways according to the ERS guidelines using either spontaneous production or induction by isotonic saline or hypertonic saline (3–5%) [20].

Classifications of inflammatory cells were done after a count of 400 non-squamous cells, and the fraction of eosinophils, lymphocytes, macrophages and neutrophils was noted. Samples with >80% non-squamous cells were classified as adequate sample [21].

Aeroallergen–immunoglobin E (IgE) sensitisation (atopy)

We defined atopy as a specific IgE >0.35 $U \cdot L^{-1}$, or a skin wheal ⩾3 mm, against ⩾1 of the following 10 most common aeroallergens in Scandinavia: birch (*Betula verrucosa*), grass (*Phleum pratense*) or ragweed (*Artemisia vulgaris*) pollen, dander from dog (*Canis familaris*), cat (*Felis domestica*), horse (*Equus caballus*), house dust mites (*Dermatophagoides farina*, *Dermatophagoides pteronyssinus*) or moulds (*Alternaria alternata/tenuis*, *Cladosporium herbarium*).

Blood samples

Leukocyte differential count, C-reactive protein (CRP) and total IgE were measured in peripheral blood using standard hospital analyses.

CT of the paranasal sinuses

Patients recruited at Næstved Hospital were invited to participate in a sub-study with non-contrast computed tomography (CT) of the nasal cavity and paranasal sinuses. The inflammatory level of each sinus (frontal, maxillary, sphenoid sinuses, and anterior and posterior ethmoid cells on each side) was graded using the Lund–Mackay score (LMS) with a score from 0 to 2 (0=no inflammation (*i.e.* normal sinus), 1=partial inflammation, 2=100% inflammation), and the osteomeatal complexes (OMC) were rated as 0 (open) or 2 (closed), resulting in a score ranging from 0 to 24 [22]. A 2016 study in 199 patients without known sinonasal disease estimated a normal LMS to be 0–5 points [23]. All scans were assessed by the first author (N.O.) who was not blinded with regards to the degree of UAS.

Statistical analyses

Data were analysed using SPSS version 27 (IBM, Chicago, USA). Skewed data are presented as the median and interquartile range (IQR). Normally distributed data are presented with mean±standard deviation (SD).

Categorical variables are presented as a count (n) and percentage (%).

Normally distributed data were analysed using Independent Samples T-test or one-way ANOVA depending on the number of groups. For skewed data, group comparisons were calculated using either the Mann–Whitney U test or the Kruskal–Wallis test. Multiple comparisons were corrected using either Tukey's or Dunn's test.

Categorical variables were compared using the Chi-squared test except for 2×2 tables. Odds ratios are reported whenever these were statistically significant. The significance level was set at <0.05, and all p-values are reported as two-tailed.

Results

Patients

A total of 271 subjects from the BREATHE study were evaluated. Of these, 180 patients met the inclusion criteria (details in figure 1). Of these, 74 patients (42%) had high UAS. Table 1 presents differences in basic demographics and clinical characteristics between patients with high and low UAS (for total cohort

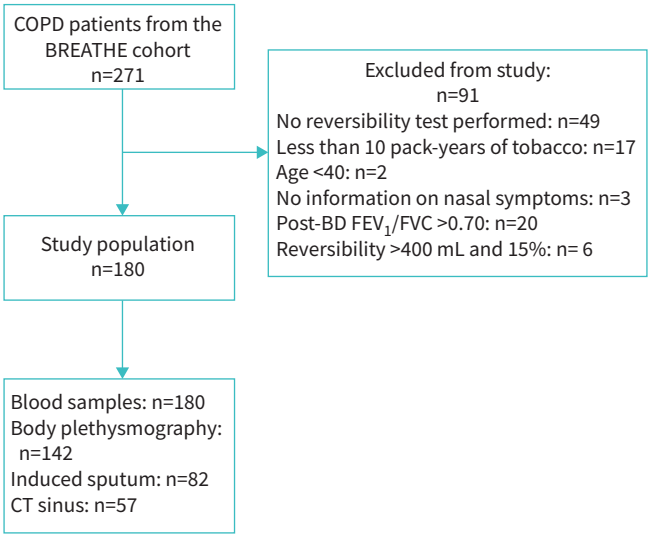

FIGURE 1 Patient flowchart. CT: computed tomography; BD: bronchodilator; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

characteristics, see supplementary table S1). High UAS was significantly associated with higher lung function (FEV_1), male sex and an increased disease burden (CAT, SNOT22).

Figure 2 shows that all types of $SNOT22_{nasal}$ symptoms were reported in both groups and that the most prevalent symptoms in both groups were "need to blow nose" and "runny nose". Fifty-four per cent of patients in the high UAS group reported a reduced sense of smell compared with 10% in the low UAS group.

Patients in the high UAS group also scored significantly higher in the "sleep and productivity" subdomain of the SNOT22 questionnaire.

High UAS was significantly associated with sputum eosinophilia (but not with elevated serum CRP levels) (table 2). We observed no differences between groups in exacerbation rates, number of frequent exacerbators, pack-years, bronchodilator responsiveness, atopy or in Lund–Mackay scores on CT of the paranasal sinuses. Furthermore, we did not observe any differences in the absolute or dichotomous levels of UAS with regard to the season of patient inclusion (p=0.953 and 0.955, respectively) or across COPD disease severity.

Inflammation

Table 2 shows that patients with high UAS displayed significantly higher blood eosinophil values both as absolute value and percentage of total leukocyte count with an odds ratio of 3.1 (95% CI: 1.6–6.2; p<0.001) for an eosinophil count $>0.30\times10^9\cdot L^{-1}$ and 2.4 (95% CI: 1.3–4.5; p<0.01) for having >3% eosinophils of the total leukocyte count. Patients in the high UAS group also showed an increased frequency of having >3% eosinophils in sputum, but this did not reach statistical significance (OR 2.5, 95% CI: 0.9–6.7, p=0.067). Figure 3a, b shows that both UAS score and CAT score increase with rising eosinophil levels, but that with the CAT score, the effect is observed from below 0.15 to between 0.15 and 0.30. In contrast, UAS stay level until the eosinophil count increases to above 0.30. When these data were stratified for the usage of inhaled corticosteroids (ICS) (supplementary figure S1a,b), the trend for UAS remained but fell below statistical significance, and the effect for CAT score was only present for those patients not receiving ICS.

Discussion

In the current study, we demonstrated that having UAS was associated with a higher COPD symptom burden and eosinophilic inflammation. To our knowledge, no prior studies have found this association.

TABLE 1 Comparison between patients with high and low upper airway symptoms

	High upper airway symptoms	Low upper airway symptoms	p-value
Subjects n	74	106	
Age years	66±9	67±8	0.745
Female sex n (%)	31 (42)	68 (64)	<0.01
BMI kg·m^{-2}	26.0±6.2	26.4±5.8	0.146
Smoking status			0.318
Former smoker	48 (65)	76 (72)	
Current smoker	26 (35)	30 (28)	
Tobacco exposure pack-years	50 (40–59)	43 (34–53)	0.141
Country			0.867
Denmark	51 (69)	75 (71)	
Sweden	23 (31)	31 (29)	
SNOT22 (total score)	29 (23–37)	14 (9–22)	<0.001
SNOT22$_{nasal}$	10 (8–13)	2 (0–4)	
Sleep and productivity sub-score (q13–19)	12 (7–18)	8 (3–13)	<0.001
CAT score	17.4±7.5	14.9±6.5	<0.05
Inhaled medication			
ICS use	31 (42)	47 (44)	0.701
Dual bronchodilator	23 (31)	26 (25)	0.408
Triple therapy	27 (37)	39 (37)	0.843
FEV$_1$ L	1.48±0.59	1.31±0.53	<0.05
FEV$_1$ % pred	53±16	52±17	0.629
FVC L	2.96±0.97	2.67±0.88	<0.05
FVC % pred	82 ±17	84±19	0.403
RV L	4.39±1.43	4.50±1.44	0.666
RV % pred	190±64	202±63	0.284
TLC L	7.20±1.66	6.90±1.53	0.235
TLC % pred	116±23	121±22	0.281
D_{LCO} mmol·min^{-1}·kPa^{-1}	4.40±1.93	3.89±1.59	0.103
D_{LCO} % pred	52±21	48±17	0.249
ΔFEV$_1$ mL	110±132	108±126	0.905
ΔFEV$_1$ %	10±12	10±12	0.947
Bronchodilator response >12%+200 mL	13 (17)	20 (19)	0.824
GOLD stage			
A	11 (15)	22 (21)	0.206
B	45 (61)	53 (50)	
C	0 (0)	4 (4)	
D	18 (24)	27 (26)	
Yearly exacerbations	21 (28)	40 (38)	0.197
⩾2 moderate/severe AECOPD/year, n (%)	18 (24)	20 (19[e])	0.377
Atopy	14 (19)	18 (17)	0.864
CT sinus score (n=57)	1.5 (0–2.25)	1 (0–2.5)	0.574
CT sinus score ⩾1	15 (71)	20 (56)	0.235

Data presented as the median and interquartile range (IQR), mean±SD, or count and percentage. BMI: body mass index; SNOT22: Sino Nasal Outcome Test 22; SNOT22$_{nasal}$: nasal domain/upper airway domain of SNOT22; CAT: COPD Assessment Test; ICS: inhaled corticosteroids; FEV$_1$: forced expiratory volume in 1 s; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; ΔFEV$_1$: increase in FEV$_1$ from baseline; GOLD: Global Initiative for Chronic Obstructive Lung Disease; AECOPD: acute exacerbations in COPD; CT: computed tomography.

Our findings support the concept of the united airways in COPD, which for a long time has been an established element in asthma pathophysiology, and is clinically relevant because treatment of allergic rhinitis or chronic rhinosinusitis with/without nasal polyps is considered a key target in achieving asthma control [24].

In COPD, there is no consensus for a similar relationship. The first report was published in 2001 by Montnémery *et al.* [5] who conducted a questionnaire-based population study in Sweden, finding that 40% of the participants with self-reported chronic bronchitis/emphysema (CBE) also reported recurrent or permanent nasal symptoms. In a follow-up study from 2008, Greiff *et al.* [25] found that the presence of self-reported nasal blockage and thick nasal discharge without CBE at the time of the original research was

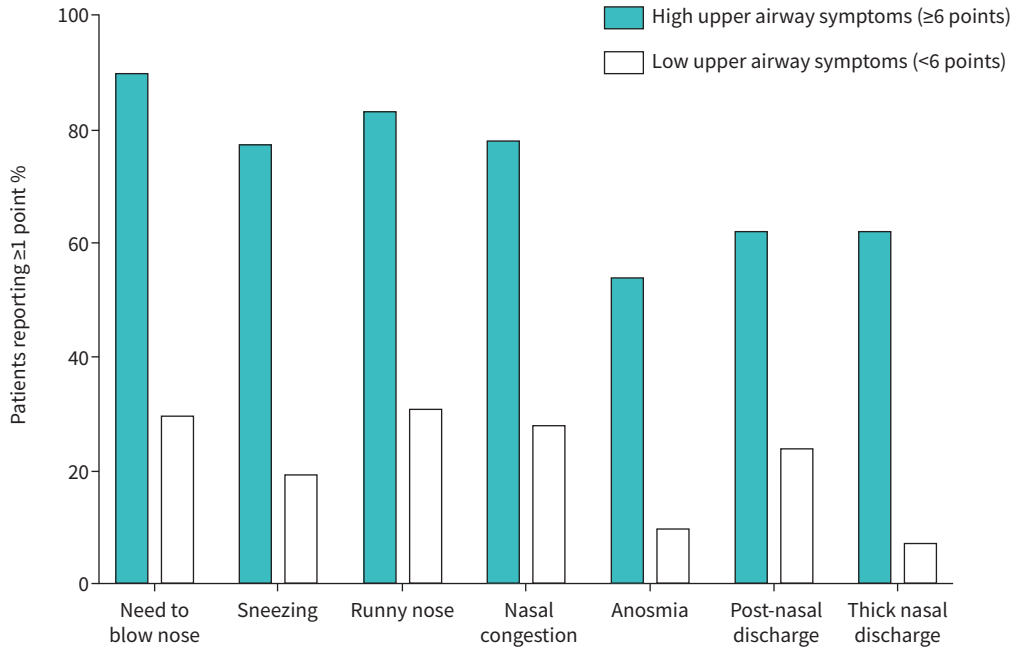

FIGURE 2 Distribution of symptoms across groups.

associated with an odds ratio of 2.3 (1.2–4.2) of developing CBE 8 years later. These studies were essential milestones in the suggestion that UAS could play a role in COPD. Still, since they relied on self-reported diagnoses, it might be difficult to rule out that some patients with self-reported COPD might be patients with concomitant asthma.

In 2004, Hurst *et al.* [6] examined a well-defined cohort of 65 patients with COPD and found that 88% of these patients reported some degree of UAS on most days of the week. These UAS were associated with reduced quality of life but not with lung function, demographic data or lower respiratory symptom scores. Another study found a prevalence of UAS of 75% in 61 patients with COPD and a correlation between sputum production and the presence of UAS [9].

In our study, we confirm the finding that patients with COPD commonly report UAS at levels above that reported in the general population, with 42% of our cohort fulfilling our criterion compared to 25% in a

TABLE 2 Markers of inflammation between groups

	High upper airway symptoms	Low upper airway symptoms	Odds ratio (95% CI)	p-value
Subjects n	74	106		
C-reactive protein mg·L^{-1}	2.9 (1.8–4.8)	2.9 (1.9–6.4)		0.330
Blood eosinophils (n=180)				
% of total leukocytes	3.0 (1.6–4.1)	2.3 (1.4–3.1)		<0.05
actual number, 10^9·L^{-1}	0.20 (0.11–0.33)	0.20 (0.10–0.21)		<0.05
n (%) patients with ⩾0.30×10^9·L^{-1}	30 (41)	19 (18)	3.1 (1.6–6.2)	<0.001
n (%) patients with ⩾3%	36 (49)	30 (29)	2.4 (1.3–4.5)	<0.01
Sputum (n=87)				
Eosinophils, % of total	1.8 (0.3–6.3)	0.5 (0–1.7)		<0.05
n (%) patients with ⩾3%	12 (40)	11 (21)	2.5 (0.9–6.7)	0.067
Neutrophils, % of total	57±26%	63±31		0.314
Macrophages, % of total	29 (15–49)	21 (5–45)		0.221
Lymphocytes, % of total	0.13 (0–0.59)	0 (0–0.19)		<0.05

Data presented as the median and interquartile range, mean±SD, or count and percentage. Between-group comparisons calculated with either Mann–Whitney U test or t-test for continuous data or Chi-square test for categorical data. Odds ratios are unadjusted.

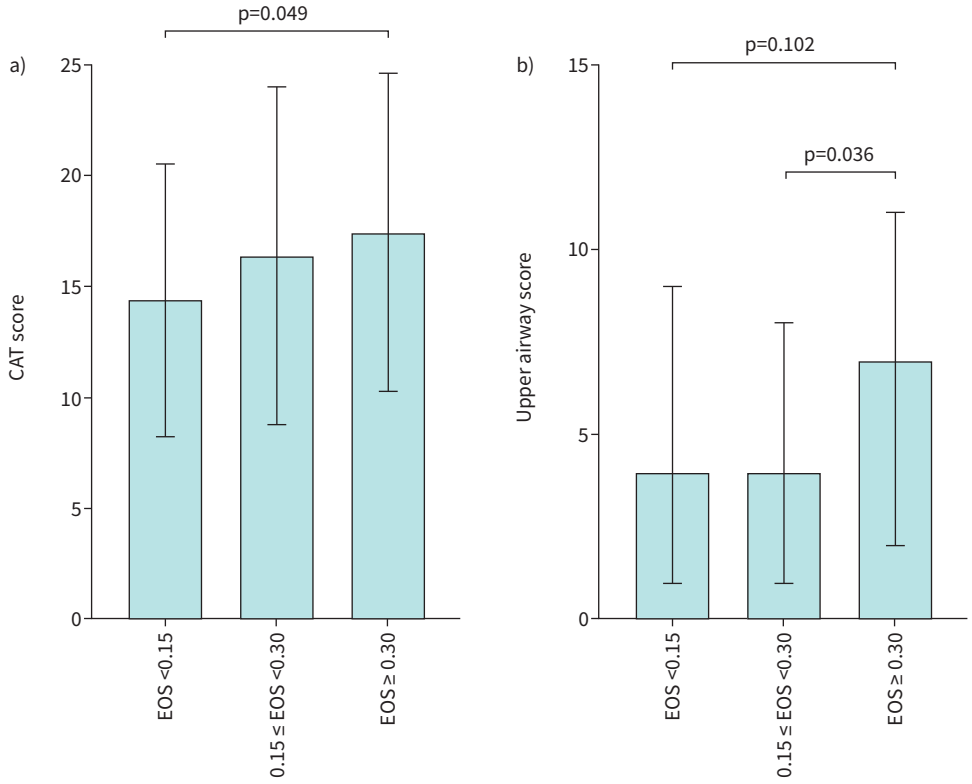

FIGURE 3 a) COPD Assessment Test (CAT) score across eosinophil (EOS) groups. b) Upper airway score across EOS groups.

US study from 2006 (self-reported rhinitis in the age group 54–85) [26]). Although the proportion of patients with UAS in our study is lower than the previously mentioned studies with prevalences reported at 88% and 75%, respectively, this could be explained by our stricter definition of these symptoms. We decided *a priori* that the UAS needed to exceed a certain threshold to be considered significant to ensure that patients either had significant symptoms in one item or light to moderate symptoms in several items. This approach is in line with studies looking at chronic rhinosinusitis, which is defined by established criteria [27]. Cross-study comparisons are difficult due to different definitions of UAS and the use of different questionnaires [28–30]. Whereas the SNOT22 is a validated and commonly used questionnaire, it was not developed to screen for UAS but to assess patients for surgery in chronic rhinosinusitis. In this study, we did not specifically evaluate the sense of smell between patient groups. However, SNOT22 has a question concerning smell, and here we found that patients in the high UAS group more frequently reported anosmia than did patients in the low UAS group (figure 2).

The SNOT22 contains several non-nasal items such as fatigue, impaired sleep, cough and reduced productivity. Such symptoms are common in COPD regardless of upper airway involvement, and COPD may confound SNOT scoring. In our study, we used the "nasal" subdomain of the SNOT22 questionnaire ($SNOT22_{nasal}$) and excluded the "cough" item to reduce this risk of confounding.

The role of eosinophils in the underlying pathogenesis of COPD has acquired increased focus. Several studies have shown that COPD patients with relative elevation of blood eosinophils [31, 32] have an increased risk of exacerbations, a greater response to ICS and a greater tendency towards recurrence of exacerbations when ICS therapy is withdrawn [32, 33]. In our study, patients with high UAS presented with higher levels of eosinophils in both blood and sputum and were three times as likely to have blood eosinophils above $0.30\times10^{9}\cdot L^{-1}$ and two and a half times more likely to have >3% eosinophils in their sputum. We did not, however, find that these patients were more likely to be of the frequent exacerbator phenotype and were not more likely to be on ICS treatment. They did, however, report significantly higher COPD symptom burden scores, and both UAS scores and CAT scores increased as the eosinophil levels rose. These findings make it necessary to question whether these patients have asthma, since UAS are

typical in asthma and asthma in old age can mimic many features of COPD. In asthma, the UAS are mostly on an allergic basis. In our study, we found no difference in the presence of atopy and the overall prevalence of 17% was also lower than in the general population and substantially lower than in a similar study where 30% of patients had atopy [34, 35]. If atopy did play a significant role, we would expect that patients included in the spring or summer time would have higher UAS scores or would more frequently be in the high UAS group. This however was not the case with both groups distributed across all four seasons and with no significant seasonal variation in UAS score.

Eosinophilia could indicate that the UAS in our study were associated with chronic rhinosinusitis. However, there is no sign that these patients had significant sinusitis, since the levels of CT-verified affection of these organs were low with a median LMS of just 1.5 (IQR 0–2.25). These values fall well below the normal values according to one study [23] and markedly lower than those found in a recent Danish study looking at chronic rhinosinusitis (CRS) in COPD patients [27].

Recently, studies have focused on treating the UAS themselves. An observational study from 2018 treated a cohort of 49 COPD patients with 8 weeks of nasal budesonide. They found that not only did the UAS decline substantially, but COPD symptom burden score such as CAT score and dyspnoea score (mMRC) diminished as well [36]. This study however was neither randomised nor placebo-controlled. To our knowledge, the only randomised study in this area is a small study by Callebaut *et al.* [37], where 27 patients were treated with 12 weeks of either nasal fluticasone furoate or placebo. In this study, 67% of the fluticasone group reported at least partial relief of nasal symptoms *versus* 54% in the placebo group. Although not perfect, these studies do show that UAS in COPD patients can be treated, and since it is well established that UAS reduce overall quality of life [38], there exists a great potential in viewing these symptoms as a treatable trait in COPD. In our study, we not only showed that patients with COPD with UAS reported higher CAT scores but also that to a greater degree they report more "secondary" symptoms such as fatigue and reduced productivity. This finding is interesting since there were no statistically significant differences in parameters which could explain this phenomenon regarding lung function, age, BMI or level of medication. We also found that UAS were not associated with disease severity assessed by Global Initiative for Chronic Obstructive Lung Disease (GOLD) class, which was in contrast to a previous study, where UAS were linked to patients with frequent exacerbations [39].

Uncovering the inflammatory profile behind the increased levels of eosinophils in more detail could lead to trials with new biological agents targeting specific cytokines or novel therapeutic options which could potentially reduce both the upper and lower respiratory symptoms in a patient group that lacks effective treatment options.

Our study is not the first to report UAS in COPD, but it is to our knowledge one of the largest cohort studies to investigate these symptoms, and since our cohort is diverse with patients from five different sites in two countries, the external validity is high. We also recruited from both primary care facilities and specialist centres, which ensures that the findings are more generally applicable in real life. Our study is further evidence that UAS is a disease feature in some patients with COPD, and it should prompt clinicians to be aware of these symptoms in order to provide the best possible patient care.

Conclusion

Upper airway symptoms are prevalent in patients with COPD and are associated with a higher burden of lower respiratory symptoms and bronchial and systemic eosinophilia. Further studies are needed to investigate inflammatory profiles and other clinical characteristics associated with these symptoms as well as more extensive randomised trials to evaluate the effect of specific treatment against upper respiratory symptoms and its impact on lower respiratory symptoms and quality of life.

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