Upper Respiratory Symptoms Worsen over Time and Relate to Clinical Phenotype in COPD

Arturo Huerta[1,3], MD, MSc, FCCP (ahuerta@clinic.ub.es), Gavin Donaldson[2], PhD (g.donaldson@imperial.ac.uk), Richa Singh, MD[2] (richa.singh@imperial.ac.uk), Alex Mackay, MD[2] (alexander.mackay@ucl.ac.uk), James Allinson, MD[2] (j.allinson@imperial.ac.uk), Simon Brill, MD[2] (s.brill@imperial.ac.uk), Beverly Kowlessar, RN[2] (b.kowlessar@imperial.ac.uk), Antoni Torres, MD, PhD[3] (atorres@clinic.ub.es), Jadwiga A Wedzicha, MD, PhD[2] (j.wedzicha@imperial.ac.uk)

Author Affiliations:
[1] Emergency Department, Medicine Section. Institut d´Investigacions Biomèdiques August Pi i Sunyer. Hospital Clinic de Barcelona. Barcelona, Spain. CibeRES 06/06/0028
[2]Airways Disease Section. Imperial College London. Royal Brompton Hospital. London, UK
[3] Institut Clínic del Tòrax, Servei de Pneumologia. Hospital Clinic de Barcelona. CibeRES 06/06/0028. Barcelona, Spain

Corresponding Author:
Arturo Huerta García, MD, MSc, FCCP
Emergency Department – Medicine Section
Institut d'Investigacions Biomèdiques August Pi i Sunyer.
Hospital Clinic de Barcelona. CIBeRES 06/06/0028
C. Villarroel 170 Esc. 4 Planta 2
Barcelona, Spain 08036
e-mail: ahuerta@clinic.ub.es
Tel: +34 932.275.400 ext 9384/ Fax: +34 932.275.549

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Keywords: COPD, Upper respiratory symptoms, Phenotype, CAT score

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Abstract

Rationale: How nasal symptoms in patients with COPD change over time and resolve during natural occurring exacerbation has never been described.

Methods: Patients in the London COPD cohort were asked about the presence of nasal symptoms (nasal discharge, sneezing, post-nasal drip (PND), blocked nose and anosmia) over an 8-year period (2005-2013) every three months at routine clinic visits at stable state and daily during exacerbations with the use of diary cards. Data was prospectively collected and in a subgroup of patients COPD Assessment Test (CAT) and human rhinovirus (HRV) identification by PCR was available. Patients were also defined as infrequent/frequent exacerbators (<2 or ≥2 exacerbations/year).

Measurements and Main Results: On 4368 visits, 209 patients with COPD were asked about their nasal symptoms. On 2033 visits, when the patients were stable, the odds ratio (OR) for nasal discharge increased by 1.32% per year (95% CI 1.19-1.45; p<0.001); sneezing 1.16% (1.05-1.29; p=0.005); post-nasal drip 1.18% (1.03-1.36; p=0.016) and anosmia 1.19% (1.03-1.37; p=0.015). At exacerbation, nasal discharge was present for 7-daysand blocked nose, sneezing and post-nasal drip increased for just 3 days; anosmia did not change. Nasal discharge was more likely in frequent exacerbators; OR 1.96 (1.17-3.28; p=0.011) and when present, COPD Assessment Test scores were higher by 1.06 units (0.32-1.80; p=0.005) when stable and 1.30 units (0.05 to 2.57; p=0.042) at exacerbation.

Conclusion: Upper airway symptoms increase over time in COPD patients and are related to the frequent exacerbator phenotype. These longitudinal changes may be due to increasing airway inflammation or the disease progression.

Abstract Word Count: 242

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality [1].The natural history of COPD is characterized by the repeated occurrence of episodes called exacerbations that are manifested by an inflammatory response, mediated predominantly by neutrophils that increase respiratory symptoms [2,3].

It is widely known that there is an association between rhinitis and asthma since 90% of patients with asthma have rhinitis and almost 30% of patients with allergic rhinitis develop asthma [4]. In COPD, nasal symptoms are not considered important, and sometimes they are neglected, as the disease is thought to be primarily due to airflow limitation in the lung [5]. However, whenever a person inhales smoke from tobacco or biomass fuels, the smoke penetrates into the whole airway from nose to distant alveoli. We have previously described the presence of chronic nasal and respiratory symptoms in COPD patients [6], the relationship of the upper airway to lower airway bacteria [7], the impact of nasal symptoms on quality of life [8] and the correlation of systemic inflammation both in upper and lower airways during exacerbation [9]. The concept that COPD is a “pan-airway” disease in COPD is gaining support with different groups publishing data that strengthen the epidemiological evidence [10,11].

However, there is no evidence that the prevalence or severity of nasal symptoms changes over time and forms part of the natural progression of the disease and neither the influence on health status, as assessed with the COPD Assessment Test (CAT) score. The concept of time-related worsening of nasal symptoms in mature population have been reported and shown that despite fairly low self-reported prevalence of these disorders in large population studies, when validated, there is a high prevalence of hyposmia and anosmia in certain groups, especially the elderly[12].

Some explanations regarding toxic exposure, head trauma, autoimmunity, or aging itself can contribute to smell impairment, with different implications concerning prognosis and possible treatment. Often, the ENT specialists are the one that identify in first place these symptoms in patients with chronic rhinosinusitis.

Thus, the aim of this study was to evaluate the evolution and impact of upper airway symptoms in a well-defined COPD cohort when stable and at exacerbation.

Methods

Study Subjects and Protocol

A total of 209 patients enrolled in the London COPD Cohort were included between March 2005 and June 2013 (with at least one year of participation in the cohort). A complete flowchart on the visits and collected data is shown in Figure 1. The post-bronchodilator forced expiratory volume in 1 second (FEV_1) of all patients was ≤80% predicted from age, height, and sex and a FEV_1/Forced Vital Capacity (FVC) ratio <0.7 [5]. A history of smoking, including smoking status and medical history were recorded. Data on nasal steroid sprays were collected from May 2010 onwards.

Definition of Exacerbation and Monitoring

Patients were also asked to record on a daily diary card any increase or occurrence in their lower airway symptoms. Dyspnoea, sputum purulence and sputum volume were defined as major symptoms and nasal discharge/congestion, wheeze, sore throat and cough were defined as minor symptoms. Exacerbations were defined as previously used by the London

COPD Cohort [13], as any change in one major symptom with at least one other (major or minor) for two consecutive days.

The annual exacerbation frequency was calculated for each patient using the number of days the patients had completed their diary between January 2005 and June 2013. Patients were then defined as infrequent exacerbators (<2 exacerbations/year) or frequent group (≥2/year) [14].

Nasal Symptoms

All subjects were asked about the presence of nasal symptoms (runny nose/nasal discharge, sneezing, post-nasal drip (PND), blocked nose or anosmia /impaired smell) in the three-months prior to their quarterly stable clinic review. From March 2011 - June 2013 (Figure 1) patients were asked to grade the severity of their nasal symptoms (0 = no symptom, 1 = very mild, 2=mild, 3=moderate, 4=severe and 5=bad as can be). At exacerbation and during recovery they were asked if there was a presence of these five nasal symptoms on each day. For the purpose of this study, runny nose and nasal discharge are considered equivalent terms.

Quality of Life Assessment Using the CAT Score

In a subgroup of patients (Figure 1), during the stable baseline state and during exacerbations, patients were asked to complete the CAT at least once under supervision in clinic and once at home. The stable state was defined when more than 35 days after and 21 days before exacerbation onset. If the baseline CAT scores before exacerbation onset were unavailable, the score during post-exacerbation stability was used.

Sputum Collection and Processing

At a number of the clinic visits (Figure 1), spontaneously expectorated sputum was collected. Quantitative Polymerase Chain Reaction (qPCR) was used to detect human rhinovirus using the ABI Prism 7500 Real-time qPCR System (Applied Biosystems) and validated primers [15].

Statistical Analysis

For the statistical analyses, Stata 13 (Stata Corp, Texas, USA) was used and data were expressed as percentages, mean ± SEM or median ± inter-quartile range. Comparisons between independent groups were made by chi-squared test, Student's *t*-test or Wilcoxon sign-rank test respectively. The correlations between the means of independent groups were evaluated with Pearson correlation test. A p-value < 0.05 was considered statistically significant.

Trends over time were first assessed in a univariate analysis with random-effect logistic regression models that allowed for repeated measures in the same individual. These trends were then assessed into a multi-variate model that included smoking status and exacerbation frequency phenotype and their interaction with time. To assess whether nasal symptoms at exacerbation rose faster overtime compared to baseline nasal symptom, we also included in the multivariate model a term describing whether the data was recorded at baseline or exacerbation and its interaction with time. Results are reported as odds ratio for a 1-year interval with 95% confidence interval.

An analysis of variance was used to compare the severity of symptom over various time periods during the onset and recovery of exacerbation with data recorded at baseline.

Random effects models that adjusted for repeated measures were used also for the analysis of the CAT score and its impact on nasal symptoms.

The Ethical Committee of the Royal Free Hospital granted approval for this study and all patients gave informed written consent.

Results

Demography

Table 1 shows the main characteristics of the 209 COPD patients included. The mean FEV_1 was 1.22 L (0.46); FEV_1 as % predicted 50.1% (SD 16.4), age was 70.7 years (SD 8.7). Of the population, 130 were male (62 %) and 66 (32%) were current smokers. A total of 13/140 (9.3%) of patients on whom data was available, have been receiving nasal corticosteroids at some time. Due to the relation between bronchiectasis and sinusitis, none of the patients included for the purpose of this study had clinical findings of bronchiectasis (large volume of sputum or coarse crepitations) during clinical history or examination.

Nasal Symptoms at Baseline and Changes over Time

Data on nasal symptoms from 209 stable patients were recorded on 2033 clinic visits. Figure 2 shows that the overall prevalence of these symptoms increased over time. In a univariate analysis all the nasal symptoms increased over time in the overall population (all symptoms, all patients, $p<0.05$), but in the multivariate analysis, the odds ratio (OR) for a runny nose/nasal discharge increased over time independently of exacerbation frequency or smoking status by 1.32% per year (95% CI 1.19-1.45; $p<0.001$); sneezing 1.16% (1.05-1.29;

p=0.005); post-nasal drip 1.18% (1.03-1.36; p=0.016) and anosmia 1.19% (1.03-1.37; p=0.015) but not blocked nose OR=1.01% (0.90-1.14; p=0.811).

However, nasal discharge was more likely in frequent exacerbators; OR 1.96 (1.17-3.28; p=0.011). Current smokers were also more likely to experience impaired smell/anosmia: OR 2.47 (1.06-5.80; p= 0.037).

Time Course of Nasal Symptoms during Exacerbations

Nasal symptoms were recorded during exacerbation between onset on day 0 and day 42 on 2197 visits; 838 visits were between 0 to +7 days of exacerbation onset. Of these 838 occasions, only the incidence of a nasal discharge and post-nasal drip increased over time, with OR 1.18 (1.09-1.29; p<0.001) and 1.20 (1.08-1.33; p<0.001) respectively, but these longitudinal changes were not significant after adjustment for smoking, frequent/infrequent exacerbator phenotype or interactions with time. The combination of the exacerbation data with the baseline data did not show any differences in the increased prevalence of nasal symptoms over time between the stable and exacerbation state.

Time Course of Nasal Severity Score

Figure 3 shows the severity of nasal symptoms at baseline, prodrome (days -7 to -1), onset (0-3 days) and during recovery from exacerbation in the overall population. In comparison with the baseline, nasal scores for runny nose/nasal discharge were higher on days 0-3 and days 4-7 (p<0.001 and p<0.001 respectively). Symptoms of a blocked nose, post-nasal drip and sneezing appeared to resolve faster than nasal discharge as scores where significantly higher on days 0-3 (p=0.006, p=0.001 and p=0.005 respectively) but by days 4-7 were not significantly different from baseline (p=0.693, p=0.069 and p=0.128 respectively). The

severity of anosmia did not change at exacerbation. The nasal severity scores were not higher than baseline on days during the prodrome (days -7 to -1) or during the later stages of exacerbation recovery, days 8-14, days 15-29 or days 29 to 42.

CAT Score and Nasal Symptoms

In a subgroup of patients (May 2011-June 2013) as stated in Figure 1, the CAT questionnaire was completed on 728 of the 2033 baseline visits and 347 of the 838 exacerbation visits in 0 to +7 days. Figure 4 shows that the CAT score were significantly different between baseline and at exacerbation in those with nasal discharge symptoms as it increased by 1.06 units (0.32-1.80; p=0.005) and by 1.30 (0.05 to 2.57; p=0.042) respectively. CAT scores were higher by 3.6 units in frequent exacerbators but there was no difference in the effect of a runny nose on the CAT score between frequent and infrequent exacerbators (p=0.062). The presence of any of the other nasal symptoms was not associated with differences in the CAT score.

Associations of Nasal Symptoms with Human Rhinovirus (HRV)

In a subgroup of patients, there were 311visits when qPCR on sputum samples collected was performed (Figure 1). HRV was detected only in 42/122 (34.4%) sputum samples when symptoms of a blocked nose were present compared to 44/188 when symptoms were absent (23.4%; p=0.034). Moreover42/122(34.4%) positive samples coincided with sneezing but only 42/188 (22.3%; p=0.019) when this symptom was absent. With a nasal discharge, the percentages were 58.2% compared to 48.2% (p=0.083); post nasal-drip 22.1% vs 21.7%; (p=0.927) and for anosmia 11.5% vs 9.0%; (p=0.485).

Discussion

This study for the first time shows that nasal symptoms in stable COPD patients increase progressively and shows their time-course during naturally occurring exacerbations. This study also relates the presence of nasal discharge to the frequent exacerbator phenotype. Moreover these data has been prospectively collected over a wide period of time (8 years) in a very well characterised cohort of COPD patients..

In a previous study by our group [6], we found a prevalence of nasal symptoms of 75%, with 52% of patients reporting nasal discharge and 45.9% reported sneezing. That study showed a trend towards increased nasal symptoms in frequent exacerbators compared to infrequent exacerbators, and that nasal symptoms were independent of smoking status. In the current study of 209 patients, we found that runny nose/nasal discharge was more common in frequent exacerbators, but none of the other symptoms were as strongly linked as this one to this phenotype. Nasal blockage and anosmia/impaired smell was more prevalent in current smokers.

Two clinical findings need to be emphasized in this study. First, the presence of nasal symptoms was different according to the frequent exacerbator phenotype, especially the presence of runny nose/nasal discharge. This may be in part due to impairment of mucociliary function in these patients and the increased mucosal inflammation in the upper airways as previously described [16].Second, although some of the patients were former smokers, the nasal symptoms continued worsening over time in both frequent and infrequent exacerbators, strengthening the hypotheses that once prolonged smoke exposure arrives at a threshold, the inflammatory stimuli cannot easily be switched-off [17].

With experimental human models of exacerbations, it is known that the majority of patients experience worsening in both upper respiratory (sneezing, post-nasal drip, runny nose/nasal discharge) and lower symptoms [18]. Our study is the first to describe the time course during exacerbations typical of those seen in the community and triggered by viruses, bacteria or pollution. As expected at exacerbations in the overall population, nasal discharge was the most common symptom (frequent and infrequent patients) at the onset, together with post-nasal drip, with both symptoms worsening during the first seven days.

Post-nasal drip, blocked nose and sneezing as symptoms appeared in the early stages of exacerbation during the first three days, but these symptoms recovered faster. This clinical evolution of nasal symptoms at exacerbation was not related to the clinical phenotype or the current or past smoking exposure.

It is important to mention that not all-nasal symptoms recorded were related to the presence of the most common respiratory virus (HRV as the cause of common cold) during exacerbations. Only nasal discharge and sneezing were consistently associated with HRV in all frequent/infrequent patients and these symptoms may be useful in identifying some exacerbations that may be early treated with anti-viral medications. This finding also agrees with studies concerning the transmission of respiratory viruses, since these agents were present in almost 50% of exacerbations[19].

Anosmia/impaired smell did not change over the time of the exacerbation even at the onset when both lower and the other upper respiratory symptoms were at their worse. No differences in anosmia were found in regards to being a frequent or infrequent exacerbator patient. However, in general population, 70.5% of women and just 29.5% of men report a worsening of anosmia either during or post-upper respiratory tract infection[20].

It is possible that since our cohort is of 62% male COPD subjects, they were less likely to report a worsening of this symptom.

During the study a subgroup of patients completed the CAT questionnaire. This is a validated eight-item questionnaire designed to assess and quantify the impact of COPD symptoms on patient health status[21] but it has been also shown to be a good tool in measuring severity [22] and recovery from exacerbations[23]. It also has two principal advantages in that it can be used in different clinical settings (primary care and second care) and shows no variability between languages[24].

Among all the nasal symptoms explored, only nasal discharge showed a rise in the CAT score, both in the stable state and during exacerbations as it was also the most prevalent symptom in our population during stable state and during exacerbations . Although it has not been properly established, a change of 1.6 units in the CAT score has been suggested as a threshold in the variation of the CAT score to arrive to the minimal clinically important difference [24].In our study we showed a rise that might not be significant, but our study opens a new study area, regarding the impact of nasal symptoms on the CAT score in COPD.

A potential limitation of the study must be addressed, as we do not have sinus CT-scans or ENT examination of all the patients (to assess the presence or absence of nasal polyps) but there is some evidence that the symptoms in both populations (with and without polyps) usually overlap[25]. We also do not have information on the possible presence of patients with the criteria for the asthma and COPD overlap syndrome as recently described by GINA-GOLD[26].

Airway bacterial colonisation (BC) is common in latest phases of COPD and is well known that sputum samples correlate with bacteria isolated from lower airways by

bronchoscopic samples[27,28].The presence of bacteria increases local inflammation of the bronchi and elevation of systemic inflammatory biomarkers [29]. However, few studies have investigated bacterial colonisation of the upper airway in COPD patients[7]. Further studies in this field are needed to clarify the pathogenics of the sinonasal symptoms.

Some strains of the common microorganisms often associated with acute exacerbations (Non-typeable *H. Influenzae, M. catarrhalis*) can form biofilms. This could lead to biofilm-associated chronic rhinosinusitis. Although, several studies aimed at preventing biofilm formation with topical antimicrobials, surfactants, loop diuretics and macrolides have been tested[30], none of these interventions have been studied in COPD patients.

A pilot study on 33 patients has recently been published on the use of nasal corticosteroids (fluticasone furoate) and showed that in patients assigned to the treatment group, there was a decrease of nasal IL-8 after 12 weeks of treatment and an amelioration of nasal symptoms [31]. However, little information is known on the frequent/infrequent phenotype in this paper or the response of eosinophilic inflammation (eotaxin response) in response to the use of nasal corticosteroids. A larger trial with more clinical characterisation in COPD patients is warranted.

In conclusion, we have shown that nasal symptoms are part of the natural evolution of COPD and that they worsen over time and are closely related to the frequent exacerbator phenotype. These symptoms should be taken into account when performing multidimensional evaluations of the patients, since they might also impact on assessment scores and health-related quality of life.

Acknowledgments: The authors want to acknowledge Siobhan George for her outstanding work doing the qPCR for rhinovirus in the cohort samples.

Table 1. Demographics on population studied at the London COPD cohort

	N = 209
Age (years)	70.7 (SD 8.7)
Gender (male) %	130 (62%)
Smoking (%) Current smoker Former smoker	 66 (31%) 143 (68%)
COPD Stage II Stage III Stage IV	 106 (50.7%) 75 (35.9%) 28 (13.4%)
FEV_1 (L)	1.22 (0.46)
FEV_1 % predicted (SD)	50.1% (16.5)
FVC (L)	2.65 (0.87)
FEV1/FVC ratio	0.47 (0.12)
Number of exacerbations in the prior year (median + interquartile range)	1.92 (1-3.1)

Figure Legends

Figure 1. Flowchart of COPD patients included, data collected and samples processed during 8-years (2005-2013) in the London COPD cohort.

Figure 2. Percentage of patient-reported symptoms over time in the London COPD Cohort. Number refers to the number of visits where patients reported having nasal symptoms.

Figure 3. Time course of nasal symptoms during exacerbations in the London COPD Cohort graded and divided by clusters of days.

Figure 4. Effect of nasal discharge during stable state and at exacerbation and its impact on the CAT score.

Figure 5. Time course of nasal symptoms during exacerbations in patients with infrequent and frequent exacerbations.* $p<0.05$, chi-squared test.

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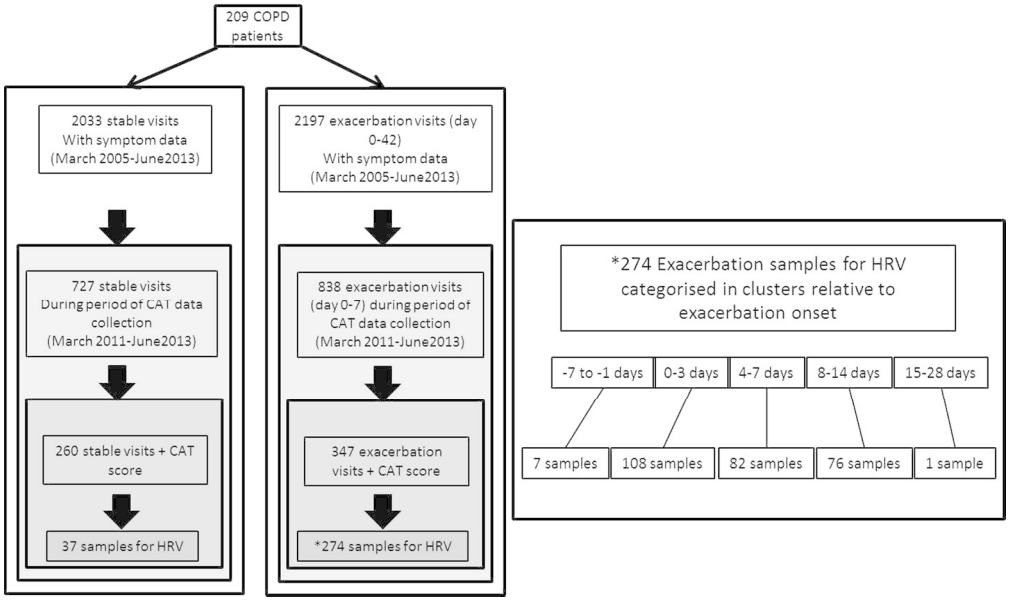

Figure 1. Flowchart of COPD patients included, data collected and samples processed during 8-years (2005-2013) in the London COPD cohort.
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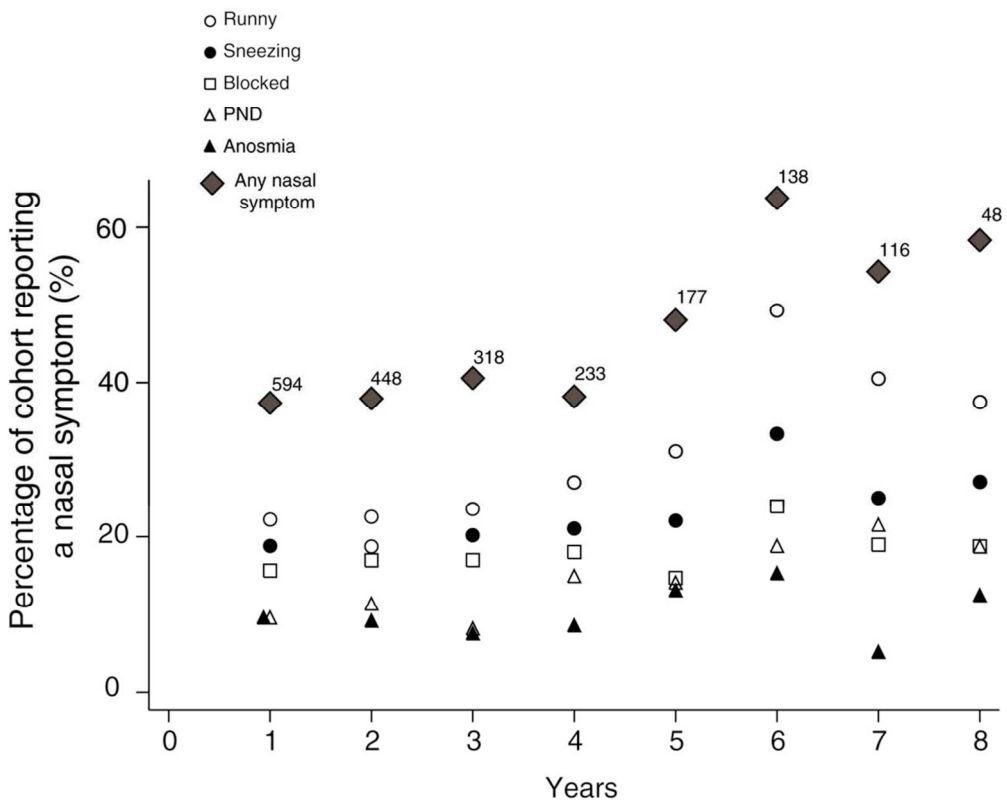

Figure 2. Percentage of patient-reported symptoms over time in the London COPD Cohort. Number refers to the number of visits where patients reported having nasal symptoms
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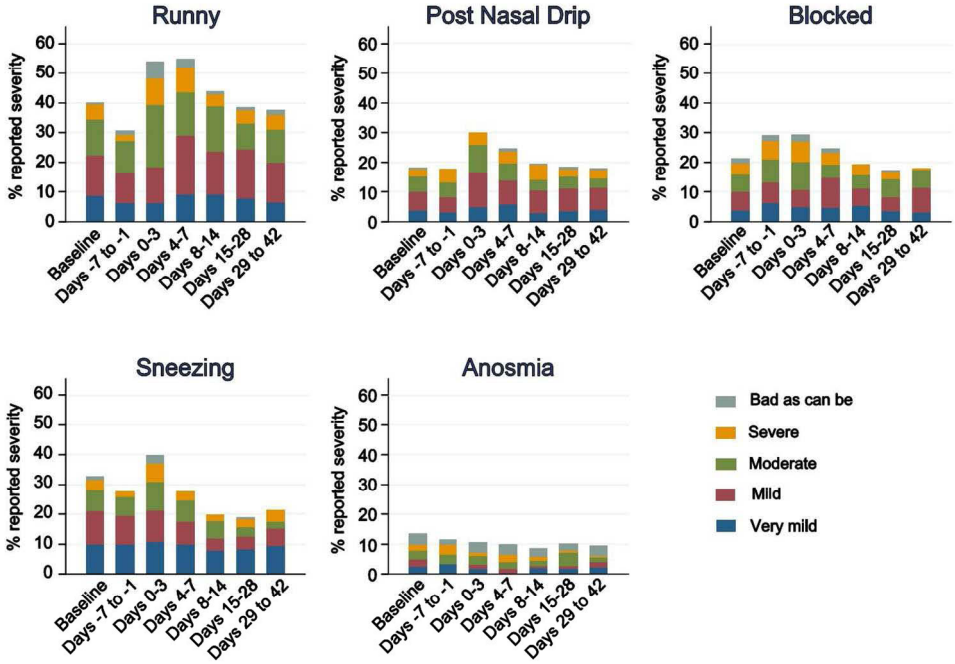

Figure. 3 Time course of nasal symptoms during exacerbations in the London COPD Cohort graded and divided by clusters of days.
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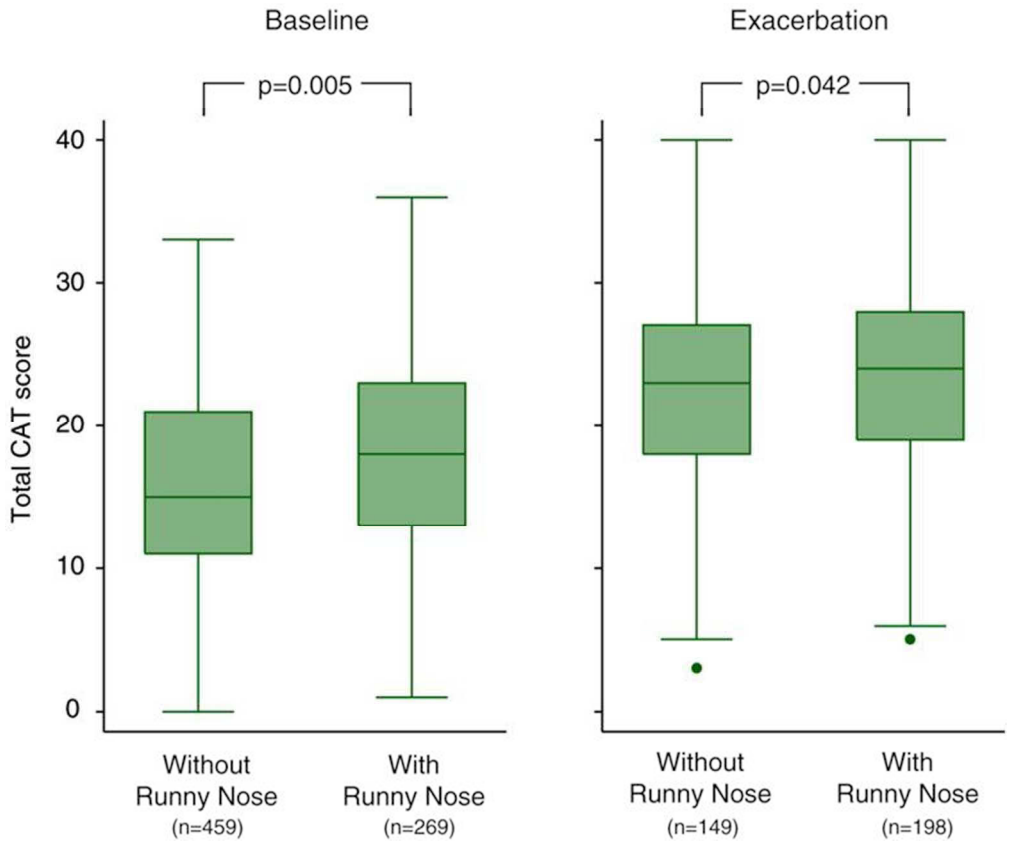

Figure 4. Effect of nasal discharge during stable state and at exacerbation and its impact on the CAT score.
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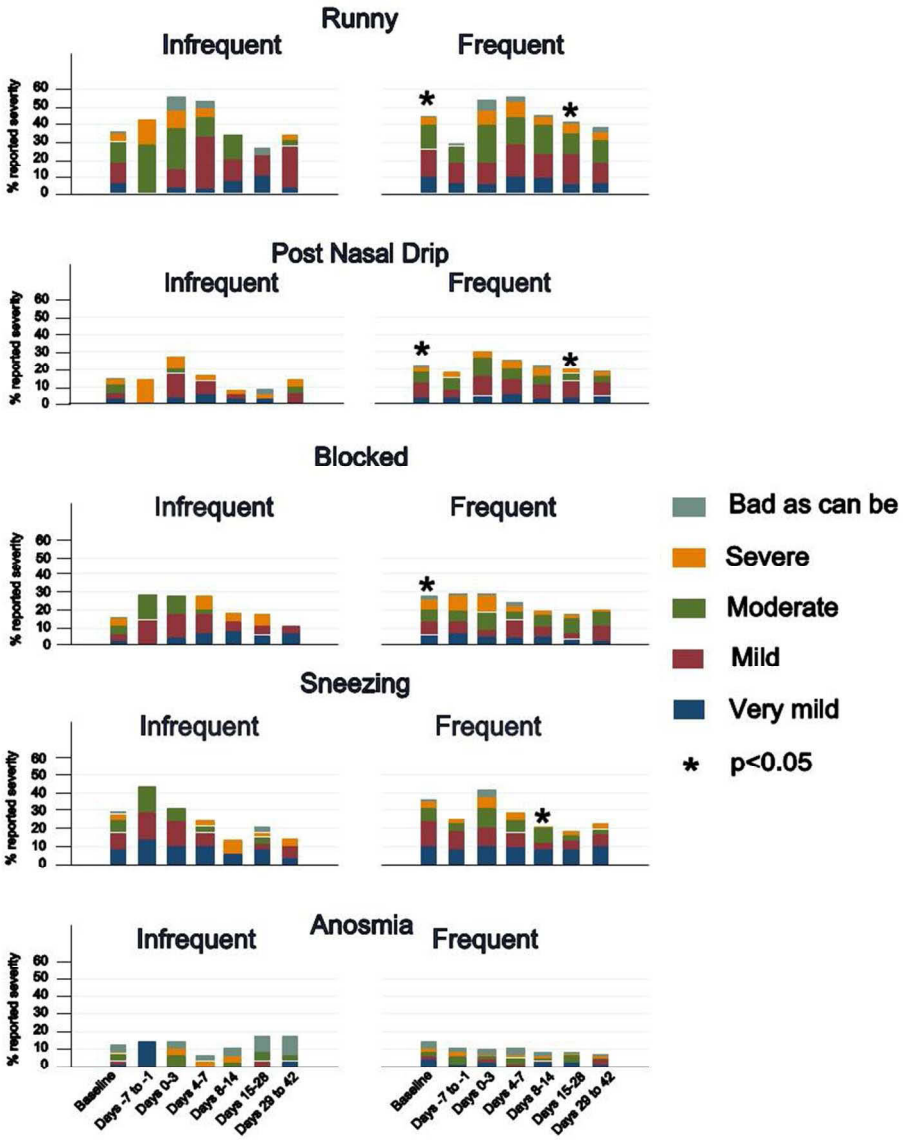

Figure. 5 Time course of nasal symptoms during exacerbations in patients with infrequent and frequent exacerbations.* p<0.05, chi-squared test.
157x190mm (150 x 150 DPI)