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ORIGINAL RESEARCH

Factors Associated with the Non-Exacerbator Phenotype of Chronic Obstructive Pulmonary Disease

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Background: Patients with chronic obstructive pulmonary disease (COPD) and no exacerbations may need less maintenance treatment and follow-up. The aim was to identify factors associated with a non-exacerbator COPD phenotype.

Methods: Cross-sectional analysis of 1354 patients from primary and secondary care, with a doctor's diagnosis of COPD. In 2014, data on demographics, exacerbation frequency and symptoms using COPD Assessment Test (CAT) were collected using questionnaires and on spirometry and comorbid conditions by record review. The non-exacerbator phenotype was defined as having reported no exacerbations the previous six months. Multivariable logistic regression with the non-exacerbator phenotype as dependent variable was performed, including stratification and interaction analyses by sex.

Results: The non-exacerbator phenotype was found in 891 (66%) patients and was independently associated with COPD stage 1 (OR [95% CI] 5.72 [3.30–9.92]), stage 2 (3.42 [2.13–5.51]) and stage 3 (2.38 [1.46–3.88]) compared with stage 4, and with CAT score <10 (3.35 [2.34–4.80]). Chronic bronchitis and underweight were inversely associated with the non-exacerbator phenotype (0.47 [0.28–0.79]) and (0.68 [0.48–0.97]), respectively. The proportion of non-exacerbators was higher among patients with no maintenance treatment or a single bronchodilator. The association of COPD stage 1 compared with stage 4 with the non-exacerbator phenotype was stronger in men (p for interaction 0.048). In women, underweight and obesity were both inversely associated with the non-exacerbator phenotype (p for interaction 0.033 and 0.046 respectively), and in men heart failure was inversely associated with the non-exacerbator phenotype (p for interaction 0.030).

Conclusion: The non-exacerbator phenotype is common, especially in patients with no maintenance treatment or a single bronchodilator, and is characterized by preserved lung function, low symptom burden, and by absence of chronic bronchitis, underweight and obesity and heart failure. We suggest these patients may need less treatment and follow-up, but that management of comorbid conditions is important to avoid exacerbations.

Keywords: COPD, exacerbations, lung function, CAT, body mass index, chronic bronchitis, sex, heart failure

Introduction

Several chronic obstructive pulmonary disease (COPD) phenotypes have been identified,[1] including the emphysema phenotype,[2] COPD with systemic inflammation[3] and the frequent exacerbator phenotype. The frequent exacerbator phenotype, characterized by more than two exacerbations per year, has received considerable attention.[4,5]

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An exacerbation is characterized by increased dyspnea and/or cough and sputum that worsens in < 14 days.[6] Exacerbations in COPD are known to be associated with disease progression, worse health-related quality of life (HRQL), and higher risk for re-exacerbations and mortality.[7–9] Risk factors associated with exacerbations are well studied and include previous exacerbations, worse lung function and presence of chronic bronchitis.[9,10]

Recent studies have reported less exacerbations and lower mortality risk with inhaled corticosteroids (ICS) in addition to long-acting muscarinic antagonists (LAMA) and long-acting beta-2-agonists (LABA) in this patient group.[11,12] However, due to increased risk of ICS side-effects, such as pneumonia,[13,14] selection of patients with low exacerbation risk may also be of clinical importance. Identifying a potential non-exacerbator phenotype could uncover a patient group requiring less medication and less monitoring from the health care providers, but such studies are lacking.

Thus, the aim of this study was to explore the prevalence of a non-exacerbator phenotype, to identify factors associated with this phenotype and to investigate if these factors differ by sex.

Materials and Methods

Data Collection

This was a cross-sectional study with data from the second cohort of the PRAXIS study, a real world observational study of COPD in central Sweden.[15] Data were collected in 2014 using patient questionnaires and medical record review. In total, 2920 patients with a doctor's diagnosis of COPD (International Classification of Diseases, tenth revision, ICD-10-code J44) were randomly selected from 14 secondary and 76 primary health care centres. The inclusion criterion was a recorded diagnosis of COPD between 2007–01-01 and 2010–12-31, and the exclusion criterion was inability (cognitive or linguistic) or unwillingness to complete the patient questionnaire. The number of participating centres was chosen to reflect the Swedish health care system, where the majority of patients with COPD are managed in primary care. The data collection process is shown in Figure 1.

The study was approved by the Ethical Board of Uppsala, Sweden (D-Nr 2010/090). Written consent was received by all participants. The data accessed complied with relevant data protection and privacy regulations.

Variables

The questionnaires provided information on sex, age, height, weight, current smoking status, chronic bronchitis, level of education, symptom burden, number of exacerbations during the previous six months and present maintenance inhaled treatment. Chronic bronchitis is defined as productive cough at least three months the previous two years,[16] and in this study chronic bronchitis denoted self-reported doctor's diagnosis of chronic bronchitis.

Age was categorized in approximate tertiles: <66, 66–69 and ≥70 years. Body mass index (BMI) was calculated and categorized based on previous knowledge of prognostic values as <22, 22–30 and ≥30 kg/m^2.[17–19] Smoking status was categorized as never smoking, ex smoking, occasional smoking and current daily smoking, and was dichotomized as current daily smoking or not in subsequent regression analyses. Level of education was divided into high and low, where high was defined as two or more years beyond Swedish compulsory school of nine years. Symptom burden was assessed by the COPD Assessment Test (CAT),[20] where CAT ≥10 indicates a high symptom burden.[21] An exacerbation was defined as an emergency visit or prescription of a course of oral glucocorticoids or antibiotics due to worsening respiratory symptoms during the previous six months and dichotomized as 0 or ≥1. Data collection in the first PRAXIS cohort was started in 2005, before the GOLD definition of frequent exacerbations previous 12 months was introduced. At this time, a shorter period of six months for exacerbation history was chosen to minimize recall bias. Level of inhaled treatment was categorized as no maintenance treatment single bronchodilator (long-acting muscarinic antagonists or long-acting beta-2-agonists), double bronchodilator (long-acting muscarinic antagonists and long-acting beta-2-agonists) or inhaled corticosteroids in any combination.

Information on spirometry data and comorbid conditions were obtained from medical records covering the period of 2005 to 2014. Ischemic heart disease (IHD), heart failure, atrial fibrillation, depression or anxiety were identified using International Classification Codes (ICD)-10. IHD was defined as any occurrence of stable angina, acute coronary syndrome, percutaneous coronary intervention or presence of a coronary artery bypass graft at baseline.

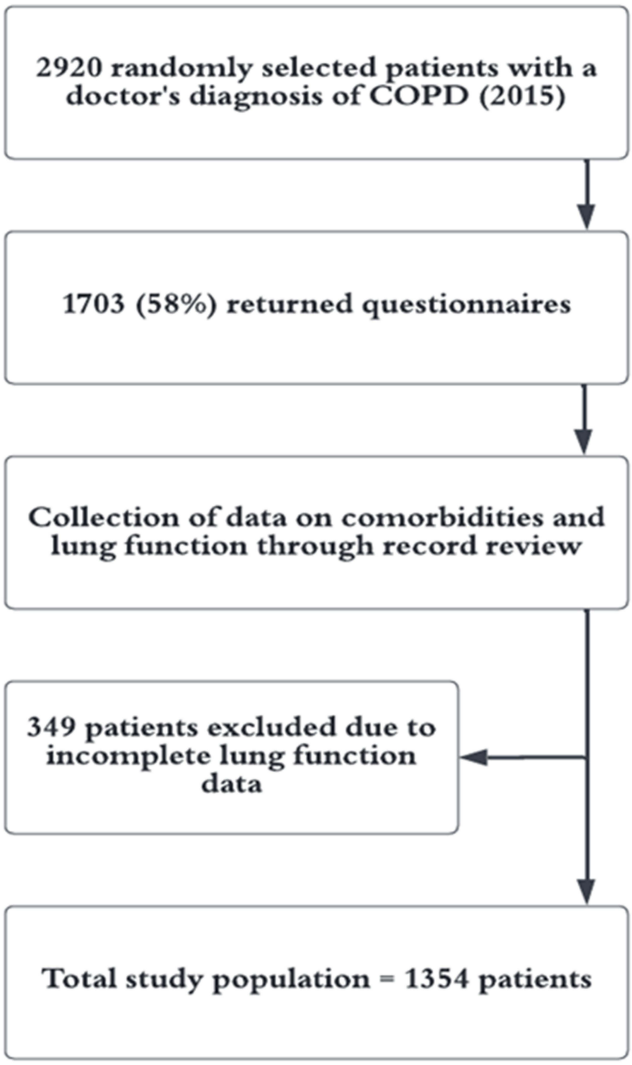

Figure 1 Flow chart describing the selection and data collection within the study.
Abbreviation: COPD, chronic obstructive lung disease.

COPD staging was based on the forced expiratory volume in one second in percentage of predicted value (FEV1% pred) according to the Global Lung Function Initiative (GLI),[22] and categorized as GOLD stage 1 (≥80%pred), stage 2 (50–79%pred), stage 3 (30–49%pred) and stage 4 (<30%pred).[21] If spirometry was repeated during the period, the highest value of FEV1%pred was used.

Statistics

Statistics were performed using IBM SPPS version 28.0 (IBM Corporation, Armonk, NY, USA). Differences in characteristics between COPD-patients with and without exacerbations were analysed using cross-tabulations and χ^2-test and presented as counts and percentages.

The proportion of patients with no exacerbations was calculated within spirometric stages and within treatment categories. Logistic regression was used to analyse associations of patient characteristics with the status of having no exacerbations the previous six months. Factors investigated, listed in Table 1 and Table 2 were chosen a-priori based on a theoretical basis and confirmed in both univariable and multivariable analysis. The multivariable model was repeated stratified by sex, and with interaction analysis using multiplicative interaction terms of sex and investigated factors. A p-value of <0.05 was considered statistically significant.

Table 1 Patient Characteristics

Variables	Patients with Exacerbations n (%) n=463 (34)	Patients without Exacerbations n (%) n=891 (66)	*p*-value
Sex			
Male	190 (41)	408 (46)	0.095
Female	273 (59)	483 (54)	Ref
Age groups			
<65	126 (28)	246 (28)	Ref
65–69	132 (29)	253 (28)	0.904
≥70	205 (44)	392 (44)	0.881
BMI groups[a]			
<22	99 (22)	138 (16)	**0.003**
22–30	242 (53)	531 (61)	Ref
≥30	113 (25)	204 (23)	0.165
COPD stage (FEV1%pred)			
Stage 1 (≥80)	76 (16)	273 (31)	**<0.001**
Stage 2 (50–79)	184 (40)	395 (44)	**<0.001**
Stage 3 (30–49)	121 (26)	184 (21)	**<0.001**
Stage 4 (<30)	82 (18)	39 (4)	Ref
CAT <10[b]	565 (66)	399 (90)	**<0.001**
Daily smoking[c]			
Never	22 (5)	32 (4)	**Ref**
Ex	304 (67)	564 (64)	**0.395**
Occasional	33 (7)	46 (5)	**0.906**
Current	93 (21)	232 (27)	**0.075**
Educational level[d]			
Low	281 (62)	495 (56)	Ref
High	175 (38)	383 (44)	0.065
COPD maintenance treatment			
No inhaled maintenance treatment	64 (14)	335 (38)	**<0.001**
LAMA or LABA	78 (17)	183 (21)	**<0.001**
LAMA and LABA	30 (7)	33 (4)	0.820
ICS in any form	291 (63)	340 (38)	Ref
Chronic bronchitis	40 (9)	40 (5)	**0.003**
Heart failure	75 (16)	71 (8)	**<0.001**
Ischemic heart disease	87 (19)	123 (14)	**0.017**
Atrial fibrillation	56 (12)	70 (8)	**0.011**
Depression or anxiety[e]	122 (27)	191 (22)	**0.033**

Notes: [a]Missing data n=27; [b]missing data n=59. [c]Missing data n=28; [d]missing data n=20; [e]missing data n=27; patient characteristics in total and distributed by presence of exacerbations or not. Statistically significant differences are presented in bold text.

Abbreviations: BMI, body mass index; COPD, chronic obstructive lung disease; FEV1%pred, forced expiratory volume in one second % of predicted; CAT, COPD assessment test; Re, reference category.

Results

In total, 1703 (58%) out of 2920 patients with a doctor's diagnosis of COPD returned the questionnaire and left written consent, whereof 1354 had available spirometry data and were included in the study. Of these, 891 (66%) reported having no exacerbations the previous six months. The proportion of patients without exacerbations decreased with severity of COPD but the non-exacerbator phenotype was present in all stages (Table 1 and Figure 2).

Overall, 47% of the population had inhaled corticosteroids in some form. The proportion of non-exacerbators was 84% in patients with no maintenance treatment, 70% with one single bronchodilator, 52% with double bronchodilators and 54% in patients with any combination including inhaled corticosteroids. In addition, the non-exacerbator phenotype more often had CAT <10 and were current daily smokers, while BMI <22 kg/m^2, chronic bronchitis, heart failure,

Table 2 Associations with the Non-Exacerbator COPD Phenotype

Variables	Unadjusted OR CI (95%)	*p*-value	Adjusted OR CI (95%)	*p*-value
Male sex	1.21 (0.97–1.52)	0.095	0.81 (0.60–1.09)	0.159
Age groups				
<65	Ref		Ref	
65–69	0.98 (0.73–1.33)	0.904	1.28 (0.90–1.81)	0.170
≥70	0.98 (0.75–1.29)	0.881	1.28 (0.92–1.80)	0.144
Current daily smoking	1.40 (1.06–1.83)	**0.017**	1.41 (1.02–1.94)	**0.036**
Level of education	1.24 (0.99–1.57)	0.066	1.21 (0.93–1.59)	0.158
BMI groups				
<22	0.64 (0.47–0.86)	**0.003**	0.68 (0.48–0.97)	**0.032**
22–30	Ref		Ref	
≥ 30	0.82 (0.63–1.08)	0.165	0.89 (0.65–1.22)	0.477
COPD stage (FEV1%pred)				
Stage 1 (≥80)	7.55 (4.78–11.9)	**<0.001**	5.72 (3.30–9.92)	**<0.001**
Stage 2 (50–79)	4.51 (2.97–6.87)	**<0.001**	3.42 (2.13–5.51)	**<0.001**
Stage 3 (30–49)	3.20 (2.05–4.99)	**<0.001**	2.38 (1.46–3.88)	**<0.001**
Stage 4 (<30)	Ref		Ref	
CAT <10	4.49 (3.20–6.30)	**<0.001**	3.35 (2.34–4.80)	**<0.001**
Chronic bronchitis	0.50 (0.32–0.78)	**0.003**	0.47 (0.28–0.79)	**0.004**
Heart failure	0.45 (0.32–0.63)	**<0.001**	0.66 (0.42–1.03)	0.064
Ischemic heart disease	0.69 (0.51–0.94)	**0.017**	0.76 (0.53–1.08)	0.122
Atrial fibrillation	0.62 (0.43–0.90)	**0.011**	0.86 (0.54–1.37)	0.515
Depression or anxiety	0.78 (0.61–1.00)	0.052	0.75 (0.57–1.00)	0.051

Notes: Results from multivariable analysis including all variables in the left column. The analyses were adjusted for sex, age, smoking, level of education, BMI, COPD stage, CAT, chronic bronchitis, heart failure, ischemic heart disease, atrial fibrillation and depression/anxiety. Statistically significant differences are presented in bold text.

Abbreviations: BMI, body mass index; CAT, COPD assessment test; CI, confidence interval; COPD, chronic obstructive lung disease; FEV1% pred, forced expiratory volume in one second % of predicted; OR, odds ratio; Ref, reference category.

ischemic heart disease, atrial fibrillation and depression/anxiety were significantly more common in patients with exacerbations (Table 1). In multivariable logistic regression, COPD stages 1–3 and CAT <10 were independently and statistically significantly positively associated, and chronic bronchitis and underweight inversely associated, with the non-exacerbator phenotype (Table 2 and Figure 3). The results remained substantially unchanged after further adjustment for level of inhaled treatment (data not shown).

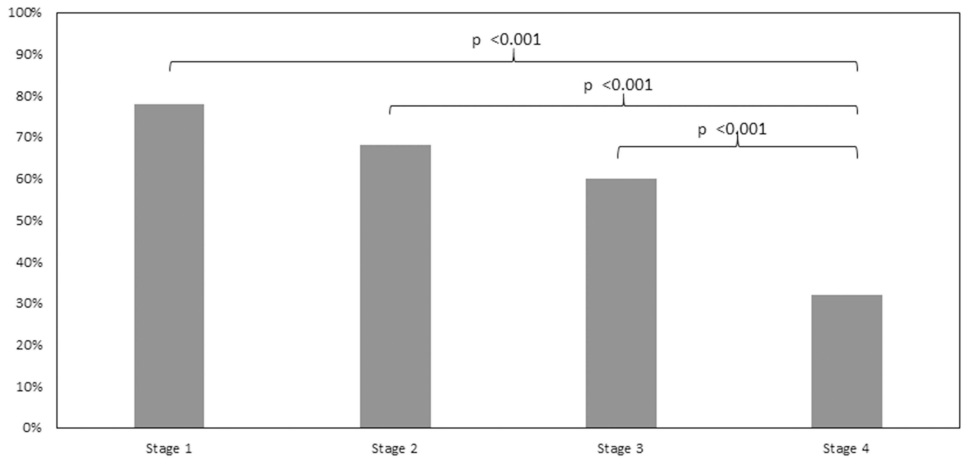

Figure 2 The non-exacerbator phenotype by severity of COPD proportions of patients with no exacerbations in every COPD stage.
Abbreviation: COPD, chronic obstructive lung disease.

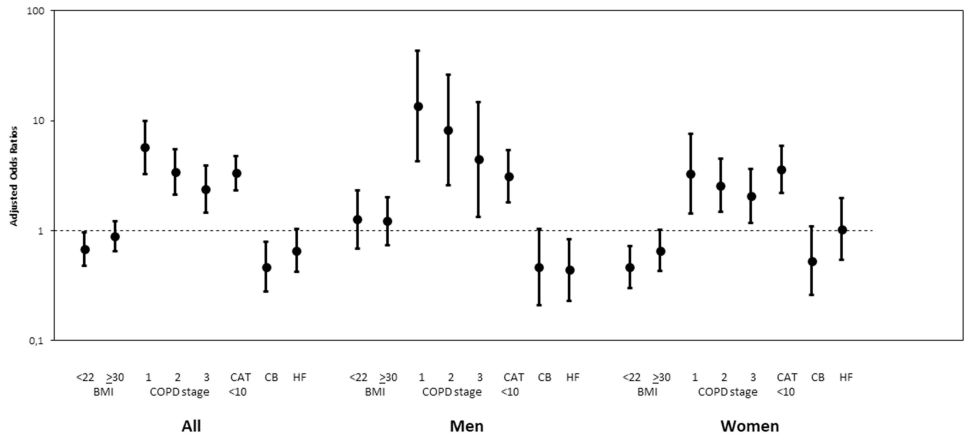

Figure 3 Factors associated with having no exacerbations in COPD results from multivariable analysis, adjusted for sex, age, smoking, level of education, BMI, COPD stage, CAT, chronic bronchitis, heart failure, ischemic heart disease, atrial fibrillation and depression/anxiety.
Abbreviations: BMI, body mass index; CAT, COPD assessment test; CB, Chronic bronchitis; HF, Heart failure.

Stratification and interaction analyses by sex showed that BMI <22 and >30 kg/m^2 were statistically significantly inversely associated with the non-exacerbator phenotype in women but not in men, and heart failure with the non-exacerbator phenotype in men but not in women (Table 3 and Figure 3). In addition, the association of COPD stage 1 with the non-exacerbator phenotype was statistically significantly of higher magnitude in men than in women (Table 3 and Figure 3).

Discussion

The primary findings of this real-world study were that a majority of patients with COPD had a non-exacerbator phenotype, and that higher lung function, lower symptom burden, and absence of chronic bronchitis and underweight were significantly associated with the non-exacerbator phenotype. Secondary findings were that factors associated with the non-exacerbator phenotype differed by sex, as absence of underweight and obesity were associated with the non-exacerbator phenotype in women but not in men, absence of heart failure was associated with the non-exacerbator phenotype in men but not in women, and the association of preserved lung function with the non-exacerbator phenotype was of higher magnitude in men compared with women.

Table 3 Differences by Sex

Variables	Men		Women		*p* for Interaction
	Adjusted OR CI (95%)	*p*-value	Adjusted OR CI (95%)	*p*-value	
BMI groups					
<22	1.27 (0.69–2.33)	0.445	0.47 (0.30–0.73)	<0.001	**0.033**
22–30	1	Ref	Ref		Ref
≥ 30	1.23 (0.74–2.02)	0.426	0.66 (0.43–1.01)	0.054	**0.046**
COPD stage					
Stage 1	13.7 (4.31–43.3)	**<0.001**	3.28 (1.43–7.56)	0.005	**0.048**
Stage 2	8.19 (2.58–26.0)	**<0.001**	2.58 (1.48–4.50)	<0.001	0.080
Stage 3	4.44 (1.34–14.7)	**0.015**	2.06 (1.17–3.64)	0.012	0.243
Stage 4	Ref		Ref		Ref
Heart failure	0.44 (0.23 to 0.83)	**0.012**	1.03 (0.54 to 1.99)	0.923	**0.030**

Notes: Multivariate analysis stratified by sex and with the results of the interaction analysis. The analyses were adjusted for sex, age, smoking, level of education, BMI, COPD stage, CAT, chronic bronchitis, heart failure, ischemic heart disease, atrial fibrillation and depression/anxiety, and the multiplicative interaction variable of sex and respective independent variable. Statistically significant differences are presented in bold text.
Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; CAT, COPD Assessment Test, COPD, chronic obstructive lung disease; Ref, reference category.

Our results are in agreement with previously reported data where the non-exacerbator phenotype seems to be stable over time.[10] The finding that patients with low CAT scores and preserved lung function were more likely to have a non-exacerbator phenotype is consistent with previous studies.[10,23,24] As exacerbations are defined as worsening of symptoms beyond normal day-to-day variation,[9] it is logical that patients with a high symptom burden already in the stable phase are more likely to perceive their symptoms as exacerbations. In addition, frequent exacerbations cause an increased decline in lung function, emphasising the importance of preventing exacerbations to preserve lung function.[25]

The prevalence of comorbidity is high in COPD patients, as 86–98% have additional comorbid disease with an average of 1.2–4 comorbid conditions.[26] Multimorbidity affects important clinical outcomes in COPD, such as HRQL, risk for exacerbations and mortality.[26,27] Chronic bronchitis could exist as a single condition or as a clinical trait or phenotype of COPD but is not always present in COPD. Its pathophysiology includes hypersecretion of mucus by goblet cells due to exposure to smoking.[21] Our finding that the absence of chronic bronchitis was independently associated with the non-exacerbator phenotype of COPD is consistent with previous research where chronic bronchitis has been associated with faster decline in lung function, decreased HRQL and frequent exacerbations. The combination of frequent exacerbations and chronic bronchitis is well known and pointed out as a COPD phenotype requiring specific treatment.[28,29] The results of our study indirectly confirm the link between chronic bronchitis and exacerbations and highlight the importance of early smoking cessation in COPD-patients to avoid development of chronic bronchitis.

Differences by sex have been observed for many aspects of COPD, such as diagnostics[30] management[31] and clinical expression of COPD.[32–34] In a study by Celli et al, women across all stages of COPD reported more dyspnoea and more exacerbations compared with men with similar lung function impairment, especially pronounced in COPD stages 1 and 2. The author suggested that women have a heightened perception of dyspnoea, which is reflected in worse HRQL.[32] We speculate that our finding of a stronger association of mild lung function impairment with a non-exacerbator COPD in men may be due to sex-related differences in perception of dyspnoea.

Our finding that BMI <22 (mainly driven by a difference in women) is inversely associated with the non-exacerbator phenotype, is consistent with previous knowledge that low BMI is a negative prognostic factor for exacerbations and mortality in COPD.[10,17,35] In a study by Lambert et al, a dose-dependent increase in dyspnoea and risk for severe exacerbations as well as a decrease in HRQL was found also with increasing BMI. Furthermore, stratification by sex showed HRQL to be more affected by obesity in women.[36] However, to our knowledge, the inverse impact of obesity on the non-exacerbator phenotype in women shown in our study has not previously been described.

Our finding that the absence of heart failure was associated with the non-exacerbator phenotype in men is consistent with previous knowledge that heart failure increases the risk for exacerbations.[37,38] Suggested reasons are the increased symptom burden with comorbid heart failure, and a possible underlying systemic inflammation.[37,39] However, we have not found any previous studies reporting differences by sex in the association of heart failure with exacerbations. We speculate that this may partly be due to the prevalence of heart failure is higher in men with COPD, as well in this study (data not shown) as in other studies.[40]

The recent IMPACT[11] and ETHOS[12] studies of the benefit of adding ICS to LAMA/LABA therapy has raised the question whether all patients with COPD should be treated with ICS to prevent risk of exacerbations and increased mortality. Interestingly, we found that a majority of patients had no exacerbations, and that the non-exacerbator phenotype was more common in patients without ICS. This is constituent with previous real-word data where exacerbations per se is the main reason for stepping up treatment.[41]

In addition, a large Swedish primary care study reported that 74% of patients with COPD and no exacerbations before study entry remained exacerbation free for 12 months, and of these 77% remained exacerbation free for 24 months.[10] Nevertheless, several studies have shown a high use of ICS treatment also in non-exacerbating patients with COPD.[11,12]

Subsequently, there is obviously a group of patients with no exacerbations where the absence of exacerbations cannot be explained by treatment with ICS. We believe that in times of high stress in the health care system, it is important to identify patients where less frequent treatment and follow-up is needed.

Finally, as for the finding that current smoking was more common in the non-exacerbator phenotype, we speculate that this is due to a healthy smoker effect where patients with no exacerbations are not motivated to quit smoking.

Strengths and Limitations

The major strength is that this study is based on real-world data from multiple centres in both primary and secondary care. The majority of the study population was based on primary care patients where mild COPD and no exacerbations is common, which increases the generalisability of the results. We also believe that our broad definition of exacerbation, including both emergency visits and steroid courses covers all relevant exacerbations without including mild airway infections or other infections treated with antibiotics with no worsening of respiratory symptoms.

A limitation is that the response rate was 58%, potentially causing response bias. However, an attrition analysis showed that responders and non-responders did not differ by sex or age. As for the responders, there was attrition due to lack of lung function data. Excluded patients did not differ by sex. Complete lung function data were not available for all older patients, which might have skewed the results. The limitation of the period of exacerbations to six months was made to minimise the risk for recall bias. On the other hand, with a longer data collection period, some of the non-exacerbators could potentially have had exacerbations. However, as significant differences were found despite the limited time study period, we believe the results are valid. The record review of comorbidity was based on ICD codes, which may underestimate the true number of comorbid conditions. Finally, the cross-sectional nature of the analyses is a limitation, as no causal associations can be proved.

Conclusion

The non-exacerbator phenotype is common, especially in patients with no maintenance treatment or a single bronchodilator, and is characterized by preserved lung function, low symptom burden and absence of chronic bronchitis. Having no exacerbations during the previous six months was also associated with absence of underweight and obesity in women, and by absence of heart failure in men.

We suggest that awareness of this group of patients is important as they may need less resource-intense management and follow-up, but that management of comorbid conditions is important to avoid exacerbations.

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Disclosure

Professor Christer Janson reports personal fees from AstraZeneca, Novartis, Boehringer Ingelheim, GlaxoSmithKline, Chiesi, Orion and Sanofi, outside the submitted work. Dr Karin Lisspers reports personal fees from Novartis, AstraZeneca, Boehringer Ingelheim, and GlaxoSmithKline, outside the submitted work. Dr Hanna Sandelowsky reports personal fees from Boehringer Ingelheim, Chiesi, Novartis, AstraZeneca, GlaxoSmithKline, and TEVA, outside the submitted work. Dr Björn Ställberg reports personal fees from AstraZeneca, Novartis, Boehringer Ingelheim, GlaxoSmithKleine, Meda/Mylan, Chiesi, and Teva, outside the submitted work. Dr Josefin Sundh reports personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi and Novartis, outside the submitted work. The authors report no other conflicts of interest related to this study.

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