ORIGINAL RESEARCH

The phenotype of concurrent chronic bronchitis and frequent exacerbations in patients with severe COPD attending Swedish secondary care units

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Background: Chronic bronchitis and previous exacerbations are both well-known risk factors for new exacerbations, impaired health-related quality of life, and increased mortality in COPD. The aim of the study was to characterize the phenotype of concurrent chronic bronchitis and frequent exacerbation in severe COPD.

Methods: Information on patient characteristics, comorbidity, and exacerbations from the previous year (total number and number requiring hospitalization) was collected from 373 patients with stage III and IV COPD attending 27 secondary care respiratory units in Sweden. Logistic regression used chronic bronchitis and frequent exacerbations (≥ 2 exacerbations or ≥ 1 hospitalized exacerbations in the previous year) as response variables. Stratification and interaction analyses examined effect modification by sex.

Results: Chronic bronchitis was associated with current smoking (adjusted odds ratio [OR] [95% CI], 2.75 [1.54–4.91]; *P*=0.001), frequent exacerbations (OR [95% CI], 1.93 [1.24–3.01]; *P*=0.004), and musculoskeletal symptoms (OR [95% CI], 1.74 [1.05–2.86]; *P*=0.031), while frequent exacerbations were associated with lung function (forced expiratory volume in 1 second as a percentage of predicted value [FEV_1% pred]) (OR [95% CI] 0.96 [0.94–0.98]; *P*=0.001) and chronic bronchitis (OR [95% CI] 1.73 [1.11–2.68]; *P*=0.015). The phenotype with both chronic bronchitis and frequent exacerbations was associated with FEV_1% pred (OR [95% CI] 0.95 [0.92–0.98]; *P*=0.002) and musculoskeletal symptoms (OR [95% CI] 2.55 [1.31–4.99]; *P*=0.006). The association of smoking with the phenotype of chronic bronchitis and exacerbations was stronger in women than in men (interaction, *P*=0.040).

Conclusion: Musculoskeletal symptoms and low lung function are associated with the phenotype of combined chronic bronchitis and frequent exacerbations in severe COPD. In women, current smoking is of specific importance for this phenotype. This should be considered in clinical COPD care.

Keywords: lung function, smoking, chronic obstructive lung disease, musculoskeletal symptoms

Introduction

In the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations, chronic bronchitis is defined as an independent disease entity with cough and sputum production for at least 3 months in 2 consecutive years, which may exist in patients with normal spirometry or may be associated with development of a fixed airflow limitation, as in chronic obstructive pulmonary disease (COPD).[1] However, not all patients with COPD have chronic bronchitis. In COPD, concurrent chronic bronchitis is associated with more rapid decline in lung function,[2] more frequent exacerbations,[3] hospital admissions,[4] worse health-related quality of life (HRQL),[5] and increased

mortality risk.[6,7] In addition, exacerbations per se are known to increase lung function decline over time[8] and to increase frequency of hospital admissions,[9] thereby generating a substantial financial burden for society.[10] Exacerbations are also known to deteriorate quality of life[11,12] and to increase the risk of mortality.[9,13,14]

Recently, attention has been paid to the specific COPD phenotype of combined chronic bronchitis and frequent exacerbations,[15] which is associated with high health care costs and resource utilization[16] and high mortality.[7] This phenotype of COPD has also been forwarded as a subgroup, where specific pharmacological treatment could reduce exacerbation risk.[17,18]

The aim of this study was to further characterize clinical factors, which are associated with the phenotype of severe COPD, with concurrent chronic bronchitis and frequent exacerbations. An additional aim was to discover if the factors associated with this phenotype differ by sex.

Methods
Data collection

Sweden has 33 hospital-based secondary care respiratory units, including departments of respiratory medicine or sections of respiratory medicine within departments of internal medicine. All 33 units were invited to participate in the present study.[5] Each respiratory unit was asked to consecutively enroll a maximum of ten patients with GOLD grade III COPD and five patients with GOLD grade IV COPD[1] during the period from May 12, 2011 to March 28, 2012, approximately matching the distribution of severe and very severe COPD in the general population.[19,20] The only exclusion criterion was an inability to complete the study on language grounds. During the patients' visits, the physician responsible for the study center collected information on sex, age, smoking history and habits, body weight and height, influenza and pneumococcal vaccination status, current pharmacological treatment, number of exacerbations, and health care visits within the past year, symptoms indicating chronic bronchitis, and presence of cardiovascular disease, diabetes, renal impairment, malnutrition, obesity/overweight, musculoskeletal symptoms, osteoporosis, or depression. Chronic bronchitis was defined as the presence of productive cough for 3 months in 2 successive years.[1] The other comorbid conditions were defined as the doctor's diagnosis, combined with pharmacological or non-pharmacological treatment of the condition. Musculoskeletal symptoms included clinical signs of muscle weakness, or ache or discomfort severe enough

to constitute the basis for maintenance treatment with medication or physiotherapy. Total number of exacerbations and number of exacerbations causing hospitalizations were noted. An exacerbation was defined as a worsening of symptoms of dyspnea and sputa beyond normal day-to-day variation, requiring increased maintenance treatment, courses of antibiotics, or oral steroids, or an emergency visit, or hospitalization.[9]

Patient information was entered in the study case record form together with data from the most recently performed spirometry. Post-bronchodilator values were used, but were substituted with pre-bronchodilator values if post-bronchodilator values were missing. The patients were classified according to GOLD[1] as COPD stage III (forced expiratory volume in 1 second as a percentage of predicted value [FEV_1% pred], 30–49) or COPD stage IV (FEV_1% pred <30 or <50 with concomitant hypoxia). Body mass index (BMI) was calculated and classified into groups defined as BMI 22 or less, BMI more than 22 but less than 31, and BMI 31 or more. Frequent exacerbations were defined as having two or more exacerbations or one or more hospitalizations due to COPD exacerbations in the most recent year.[1] Based on these criteria, the patients were categorized into four groups: 1) no chronic bronchitis or frequent exacerbations; 2) frequent exacerbations but no chronic bronchitis; 3) chronic bronchitis but no frequent exacerbations; and 4) chronic bronchitis and frequent exacerbations. The outcomes of primary interest were the associations with the category of concurrent chronic bronchitis and frequent exacerbations.

Statistics

Statistical analyses were performed using IBM Statistics SPSS version 22.0 (IBM Corporation, Armonk, NY, USA). Student's t-test was used to investigate differences in continuous variables and the χ^2 test was used to investigate differences in categorical variables. Binary logistic regression analyses with chronic bronchitis and respectively frequent exacerbations as response variables were performed. Multinominal regression was used when the response variable included the four categories related to chronic bronchitis and frequent exacerbations. Univariate regression analyses examined the potential explanatory variables of sex, age, FEV_1% pred, current smoking status, BMI (three groups), cardiovascular disease, diabetes, renal impairment, musculoskeletal symptoms, osteoporosis, depression, and in the binary logistic regression, frequent exacerbations and respectively chronic bronchitis. No a priori assumptions were made, and

thus, multivariate logistic regression analyses included variables with statistically significant associations in univariate logistic regression. The multivariate logistic regression model was repeated with adjustment for treatment with long-acting muscarinic antagonists and/or combined long-acting beta-2-agonists and inhalation corticosteroids, and with adjustment for vaccinations. To investigate differences between male and female patients, the multinominal multivariate logistic regression model analysis was performed stratified by sex. Separate interaction analysis investigated potential modification of effect by sex, using interaction terms for this variable with the explanatory variables included in the multivariate analysis. In all analyses, a *P*-value below 0.05 was considered statistically significant.

Ethics

The current study was conducted as a non-interventional trial, in accordance with EU directive 2001/20/EC and the Declaration of Helsinki. The study protocol was reviewed and approved by the Regional Ethical Review Board of Umeå University (Dnr 2011-10-31M). Written consent was given by all patients.

Results
Data collection

In total, data were collected from 383 patients. Of these, ten patients did not fulfill the inclusion criterion of a FEV_1 below 50% of predicted value and were excluded from further analyses. Post-bronchodilator values were missing for 161 patients, and were replaced with pre-bronchodilator values.

Patient characteristics

Patient characteristics, distributed on having chronic bronchitis or not, and frequent exacerbations or not, are presented in Table 1. In summary, patients with chronic bronchitis were more often current smokers, had frequent exacerbations, and had musculoskeletal symptoms, compared with those without chronic bronchitis. Patients with frequent exacerbations more often had COPD stage IV, chronic bronchitis, diabetes, and musculoskeletal symptoms than those patients with infrequent exacerbations.

Of the patients, 35.7% had neither chronic bronchitis nor frequent exacerbations, 27.3% had frequent exacerbations but no chronic bronchitis, 15.0% had chronic bronchitis but

Table 1 Patient characteristics by chronic bronchitis and frequent exacerbations

Patient characteristics	Chronic bronchitis		*P*-value	Frequent exacerbations		*P*-value
	No (n=235)	Yes (n=138)		No (n=189)	Yes (n=184)	
Sex						
Male	105 (44.7%)	60 (43.5%)	Ref	99 (52.4%)	109 (59.2%)	Ref
Female	130 (55.3%)	78 (56.5%)	0.821	90 (47.6%)	75 (40.8%)	0.182
Age	71.2 (±8.31)	71.3 (±7.02)	0.919	71.2 (±7.79)	71.3 (±7.93)	0.938
Smoking habits						
Never or ex-smoker	209 (88.9%)	103 (74.6%)	Ref	155 (82.0%)	156 (85.2%)	Ref
Current smoker	26 (11.1%)	35 (25.4%)	<0.0001	34 (18.0%)	27 (14.7%)	0.399
COPD stage						
III	170 (72.3%)	89 (64.5%)	Ref	150 (79.4%)	109 (59.2%)	Ref
IV	65 (27.7%)	49 (35.5%)	0.112	39 (20.6%)	75 (40.8%)	<0.0001
FEV_1% pred	35.2 (±8.57)	34.0 (±8.87)	0.176	56 (29.6%)	82 (44.6%)	0.003
Body mass index						
≤22.0	66 (28.1%)	48 (34.8%)	0.155	50 (26.5%)	64 (34.8%)	0.155
>22.0, ≤30.0	139 (59.1%)	72 (52.2%)	Ref	110 (58.2%)	101 (54.9%)	Ref
>30.0	30 (12.8%)	18 (13.0%)	0.658	29 (15.3%)	19 (10.3%)	0.300
Frequent exacerbations	102 (43.4%)	82 (59.4%)	0.003	–	–	–
Chronic bronchitis	–	–	–	52 (29.6%)	114 (44.6%)	0.003
Cardiovascular disease	140 (59.6%)	83 (60.1%)	0.914	109 (57.7%)	114 (62.0%)	0.399
Diabetes	23 (9.8%)	17 (12.3%)	0.446	20 (10.6%)	20 (10.9%)	0.928
Renal impairment	9 (3.8%)	5 (3.6%)	0.919	7 (3.7%)	7 (3.8%)	0.959
Musculoskeletal symptoms	45 (19.1%)	45 (32.6%)	0.003	36 (19.0%)	54 (29.3%)	0.020
Osteoporosis	57 (24.3%)	46 (33.3%)	0.058	43 (22.8%)	60 (32.6%)	0.033
Depression	33 (14.0%)	29 (21.0%)	0.081	27 (14.3%)	35 (19.0%)	0.219

Note: Data presented as numbers (%) of characteristics or mean (± standard deviations) as compared with the remaining study population.
Abbreviations: n, number of patients; FEV_1% pred, forced expiratory volume in 1 second as a percentage of predicted value; Ref, reference.
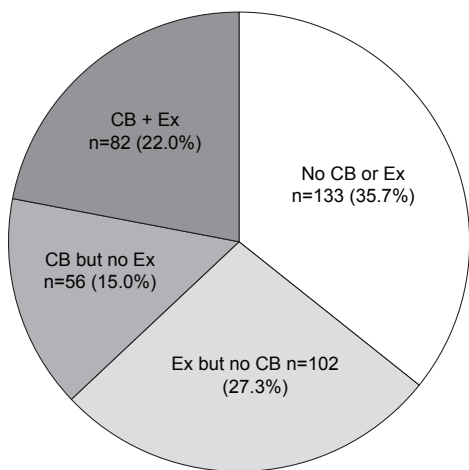
Figure 1 Categories of the response variable in multi-nominal logistic regression.
Note: Data presented as numbers (percentages) of the total study population.
Abbreviations: CB, chronic bronchitis; Ex, frequent exacerbations; No CB or Ex, no chronic bronchitis and no frequent exacerbations; CB + Ex, both chronic bronchitis and frequent exacerbations.

not frequent exacerbations, and 22.0% had the phenotype of both chronic bronchitis and frequent exacerbations (Figure 1). Patients with frequent exacerbations but no chronic bronchitis had COPD stage IV more often compared with the reference group of patients with no chronic bronchitis

and no frequent exacerbations. Patients with chronic bronchitis without frequent exacerbations were more likely to be current smokers, and patients with combined chronic bronchitis and frequent exacerbations more often had COPD stage IV, musculoskeletal symptoms, and osteoporosis (Figure 2).

Logistic regression analyses

The main results of the binary logistic regression analyses are presented in Table 2. Current smoking, frequent exacerbations, and musculoskeletal symptoms were associated with chronic bronchitis, whereas $FEV_1\%$ pred and chronic bronchitis were associated with frequent exacerbations. The main results of the multinominal logistic regression analyses are presented in Table 3 and Figure 3. Current smoking was associated with having chronic bronchitis without frequent exacerbations. Lower $FEV_1\%$ pred and musculoskeletal symptoms were associated with the combined phenotype of chronic bronchitis and frequent exacerbations. The results of the binary and multinominal logistic regression analyses did not change considerably with further adjustment for maintenance therapy or vaccination status (data not shown).
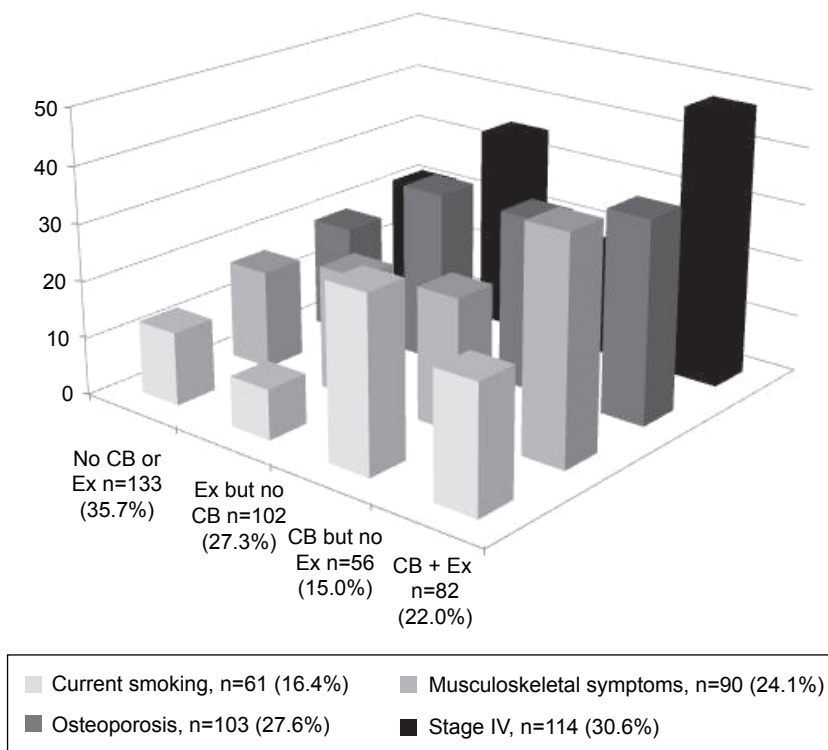

Figure 2 Clinical characteristics in different phenotypes.
Note: Proportion of clinical characteristics in different phenotypes, expressed as percentages.
Abbreviations: CB, chronic bronchitis; Ex, frequent exacerbations; No CB or Ex, no chronic bronchitis and no frequent exacerbations; CB + Ex, both chronic bronchitis and frequent exacerbations.

Table 2 Logistic regression analyses

Explanatory variables	Chronic bronchitis Unadjusted OR (95% CI)	P-value	Chronic bronchitis Adjusted OR (95% CI)	P-value
Current smoker	2.73 (1.56–4.78)	<0.0001	2.75 (1.54–4.91)	0.001
Frequent exacerbations	1.91 (1.25–2.93)	0.003	1.93 (1.24–3.01)	0.004
Musculoskeletal symptoms	2.04 (1.26–3.31)	0.004	1.74 (1.05–2.86)	0.031
	Frequent exacerbations Unadjusted OR (95% CI)	P-value	Frequent exacerbations Adjusted OR (95% CI)	P-value
FEV$_1$% pred	0.96 (0.93–0.98)	<0.0001	0.96 (0.94–0.98)	0.001
Chronic bronchitis	1.91 (1.25–2.93)	0.003	1.73 (1.11–2.68)	0.015
Musculoskeletal symptoms	1.77 (1.09–2.86)	0.021	1.51 (0.91–2.53)	0.114
Osteoporosis	1.64 (1.04–2.60)	0.034	1.29 (0.79–2.10)	0.314

Note: In the multivariate analyses, all variables with a statistically significant association in the univariate analyses were included and presented in the table.
Abbreviations: OR, odds ratio; CI, confidence interval; FEV$_1$% pred, forced expiratory volume in 1 second as a percentage of predicted value.

Sex differences

The multivariate multinominal regression analyses stratified by sex are shown in Table 4. In men, lower FEV$_1$% pred was associated with the combined phenotype of chronic bronchitis and frequent exacerbations. In women, current smoking and osteoporosis were associated with chronic bronchitis without frequent exacerbations, and current smoking and musculoskeletal symptoms were associated with chronic bronchitis and frequent exacerbations. The interaction analyses showed that the association of musculoskeletal symptoms in patients with chronic bronchitis but no frequent exacerbations, and the association of current smoking with the combined phenotype of chronic bronchitis and frequent exacerbations, was stronger in women than in men (Table 4).

Discussion

The most important finding in our study is that the phenotype of having both chronic bronchitis and frequent exacerbations is characterized by lower lung function and musculoskeletal symptoms. We find it interesting that musculoskeletal symptoms were associated with chronic bronchitis and with the phenotype of chronic bronchitis and frequent exacerbations. We are not aware of any previous study showing the association of musculoskeletal symptoms with these phenotypes.

For practical reasons, we defined musculoskeletal symptoms as a doctor's diagnosis of muscle weakness, or muscle ache or discomfort enough to cause maintenance treatment with medication or physiotherapy. Skeletal muscle dysfunction as measured by quadriceps strength is prevalent in approximately a third of all COPD patients, increasing by disease severity.[21] Indeed, the updated American Thoracic Society/European Respiratory Society (ATS/ERS) statement on limb muscle dysfunction in COPD emphasizes that muscle dysfunction influences physical activity, exercise tolerance, quality of life, and mortality.[22] Several pathophysiological explanations for musculoskeletal dysfunction in COPD have been suggested, and the underlying cause is often multifactorial. Reduced activity, malnutrition, systemic steroids, hormone imbalance, hypoxia, oxidative stress, and inflammation can all lead to muscle weakness.[22,23] It is known that several pro-inflammatory cytokines can cause catabolism and muscle atrophy in chronic diseases.[24] Moreover, systemic inflammation, as assessed by highly sensitive C-reactive protein, fibrinogen, and interleukin-6 in blood, is associated with a decreased level of physical activity in COPD, possibly indicating that

Table 3 Multinominal regression

Variables	No chronic bronchitis, no frequent exacerbations (n=133)	No chronic bronchitis, but frequent exacerbations (n=102)	P-value	Chronic bronchitis, but no frequent exacerbations (n=56)	P-value	Chronic bronchitis, and frequent exacerbations (n=82)	P-value
Current smoker	Ref	0.67 (0.28–1.58)	0.359	2.94 (1.35–6.39)	0.006	1.84 (0.86–3.94)	0.115
FEV$_1$% pred	Ref	0.97 (0.94–1.00)	0.079	1.01 (0.97–1.05)	0.617	0.95 (0.92–0.98)	0.002
Musculoskeletal symptoms	Ref	1.20 (0.61–2.37)	0.600	1.08 (0.48–2.42)	0.858	2.55 (1.31–4.99)	0.006
Osteoporosis	Ref	1.60 (0.85–3.00)	0.142	1.82 (0.86–3.84)	0.116	1.59 (0.82–3.10)	0.172

Note: In the multivariate analysis, all variables with a statistically significant association in the univariate analyses were included and presented in the table. Data are presented as adjusted OR (95% CI).
Abbreviations: OR, odds ratio; CI, confidence interval; FEV$_1$% pred, forced expiratory volume in 1 second as a percentage of predicted value; Ref, reference.
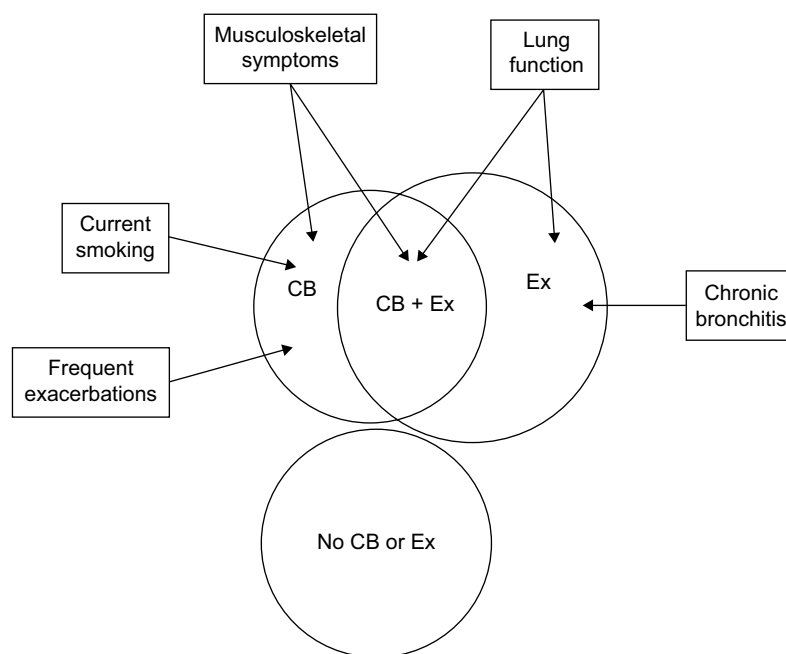
Figure 3 COPD phenotypes and patient characteristics.
Note: Venn diagram showing the proportional distribution of different phenotypes in the study population, and the associations of different patient characteristics in logistic regression analyses.
Abbreviations: CB, chronic bronchitis; Ex, frequent exacerbations; No CB or Ex, no chronic bronchitis and no frequent exacerbations; CB + Ex, both chronic bronchitis and frequent exacerbations.

inflammation in itself could initiate muscle dysfunction.[25,26] Muscle fatigue has also been shown to be more pronounced in smokers than in ex-smokers,[27] which supports the hypothesis of active inflammation as an important explanation to muscle dysfunction in COPD.

The second most important finding in our current study was that current smoking appears to increase the likelihood of having the phenotype with the combination of chronic bronchitis and frequent exacerbations in women but not in men. Female sex is known to be an independent risk factor for having frequent exacerbations,[7] but to our knowledge, sex differences in how other risk factors influence the risk of chronic bronchitis and frequent exacerbations have not been discussed previously.

Women seem to be more sensitive to a given amount of tobacco smoke exposure,[28] and in addition, estradiol-mediated differences in tobacco-smoke metabolism by up-regulation of cytochrome P450 enzymes have been suggested.[29]

Our results also confirm the previous well-known association between chronic bronchitis and exacerbations in COPD,[3,7,30,31] and the fact that frequent exacerbations are mainly influenced by lower lung function,[7] and that chronic bronchitis is mainly influenced by current smoking.[3] However, our study adds yet one more clinical dimension by emphasizing the phenotype of having the combination of chronic bronchitis and frequent exacerbations. The group of patients with this phenotype constitutes a minority of the study

Table 4 Sex differences in multinominal regression

Explanation variables	Male Adjusted OR (95% CI)	P-value	Female Adjusted OR (95% CI)	P-value	P-value interaction
Both chronic bronchitis and frequent exacerbations					
Current smoker	0.65 (0.19–2.28)	0.502	3.86 (1.31–11.4)	0.015	0.040
FEV$_1$% pred	0.91 (0.86–0.96)	0.001	0.97 (0.93–1.02)	0.202	0.075
Musculoskeletal symptoms	2.74 (0.86–8.77)	0.090	2.45 (1.06–5.66)	0.036	0.810
Osteoporosis	1.19 (0.32–4.42)	0.798	1.91 (0.85–4.32)	0.120	0.275
Chronic bronchitis but no frequent exacerbations					
Current smoker	2.47 (0.86–7.11)	0.095	4.28 (1.26–14.5)	0.020	0.339
FEV$_1$% pred	1.01 (0.95–1.07)	0.812	1.01 (0.96–1.07)	0.741	0.972
Musculoskeletal symptoms	0.20 (0.02–1.74)	0.144	2.13 (0.78–5.80)	0.139	0.028
Osteoporosis	0.68 (0.13–3.68)	0.657	3.25 (1.23–8.64)	0.018	0.474

Note: Results from multi-nominal multivariate regression analyses stratified by sex.
Abbreviations: OR, odds ratio; CI, confidence interval; FEV$_1$% pred, forced expiratory volume in 1 second as a percentage of predicted value.

population, approximately a fifth in our study. Nevertheless, the combined phenotype contributes to higher health care costs, higher resource utilization,[16] and increased mortality,[7] which motivates a focus on optimizing COPD care in this specified subgroup. Interestingly, special attention has been given to add-on treatment to COPD patients with chronic bronchitis and frequent exacerbations, where the PDE4 inhibitor roflumilast has been shown to reduce hospitalized exacerbations.[18] Another possibility might be maintenance therapy with macrolides for reduction of exacerbation frequency.[32] However, more studies are needed to further explore the target group and the long-term effects.

A strength of the current investigation is that it is a multicenter study of patients from almost all the secondary care respiratory units in Sweden with data on important clinical factors including several comorbid conditions. A potential limitation is that the comorbid conditions were defined as demanding pharmacological or non-pharmacological treatment of the specific comorbid condition. Hypothetically, this could mean that milder forms of symptoms related to the comorbid conditions have been overlooked. In addition, the term musculoskeletal symptoms could cover a variety of conditions of different character. However, the fact that the definition was based on a doctor's diagnosis combined with pharmacological or non-pharmacological treatment should ensure that only clinically relevant conditions were involved. Future studies should be directed to characterize the musculoskeletal symptoms in greater detail, and should also include measures of muscle strength or physical capacity.

Conclusion

Lower lung function and musculoskeletal symptoms are associated with the phenotype of chronic bronchitis and frequent exacerbations in patients with severe COPD. In women, unlike in men, current smoking also influences this combined phenotype. These factors should be considered in clinical COPD care.

Disclosure

The authors report no conflicts of interest in this work.

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