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 [FEV₁% 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 FEV₁% 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 time6 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 life11,12 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 utilization16 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 fac-
tors 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 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 vaccina-
tion 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 symp-
toms, 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 pharma-
cological or non-pharmacological treatment of the condi-
tion. 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.6

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 GOLD1 as COPD stage III
(forced expiratory volume in 1 second as a percentage of
predicted value [FEV1 % pred], 30–49) or COPD stage IV
(FEV1 % 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 bron-
chitis 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 con-	inuous variables and the χ2 test was used to investigate dif-
fferences 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 vari-
able included the four categories related to chronic bronchitis
and frequent exacerbations. Univariate regression analyses
examined the potential explanatory variables of sex, age,
FEV1 % pred, current smoking status, BMI (three groups),
cardiovascular disease, diabetes, renal impairment, musculo-
skeletal 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 \( \text{FEV}_1 \) 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** |
| **Sex** | No (n=235) | Yes (n=138) | | No (n=189) | Yes (n=184) | |
| 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; \( \text{FEV}_1 \) % pred, forced expiratory volume in 1 second as a percentage of predicted value; Ref, reference.
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).
Table 2 Logistic regression analyses

<table>
<thead>
<tr>
<th>Explanatory variables</th>
<th>Chronic bronchitis Unadjusted OR (95% CI)</th>
<th>P-value</th>
<th>Chronic bronchitis Adjusted OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoker</td>
<td>2.73 (1.56–4.78)</td>
<td>&lt;0.0001</td>
<td>2.75 (1.54–4.91)</td>
<td>0.001</td>
</tr>
<tr>
<td>Frequent exacerbations</td>
<td>1.91 (1.25–2.93)</td>
<td>0.003</td>
<td>1.93 (1.24–3.01)</td>
<td>0.004</td>
</tr>
<tr>
<td>Musculoskeletal symptoms</td>
<td>2.04 (1.26–3.31)</td>
<td>0.004</td>
<td>1.74 (1.05–2.86)</td>
<td>0.031</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequent exacerbations Unadjusted OR (95% CI)</th>
<th>P-value</th>
<th>Frequent exacerbations Adjusted OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV,% pred</td>
<td>0.96 (0.93–0.98)</td>
<td>&lt;0.0001</td>
<td>0.96 (0.94–0.98)</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>1.91 (1.25–2.93)</td>
<td>0.003</td>
<td>1.73 (1.11–2.68)</td>
</tr>
<tr>
<td>Musculoskeletal symptoms</td>
<td>1.77 (1.09–2.86)</td>
<td>0.021</td>
<td>1.51 (0.91–2.53)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>1.64 (1.04–2.60)</td>
<td>0.034</td>
<td>1.29 (0.79–2.10)</td>
</tr>
</tbody>
</table>

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,% pred, forced expiratory volume in 1 second as a percentage of predicted value.

Sex differences

The multivariate multinomial regression analyses stratified by sex are shown in Table 4. In men, lower FEV\textsubscript{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

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

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,% pred, forced expiratory volume in 1 second as a percentage of predicted value; Ref, reference.
inflammation in itself could initiate muscle dysfunction.\textsuperscript{25,26} Muscle fatigue has also been shown to be more pronounced in smokers than in ex-smokers,\textsuperscript{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,\textsuperscript{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,\textsuperscript{28} and in addition, estradiol-mediated differences in tobacco-smoke metabolism by up-regulation of cytochrome P450 enzymes have been suggested.\textsuperscript{29}

Our results also confirm the previous well-known association between chronic bronchitis and exacerbations in COPD,\textsuperscript{3,7,30,31} and the fact that frequent exacerbations are mainly influenced by lower lung function,\textsuperscript{7} and that chronic bronchitis is mainly influenced by current smoking.\textsuperscript{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

<table>
<thead>
<tr>
<th>Explanation variables</th>
<th>Male</th>
<th>P-value</th>
<th>Female</th>
<th>P-value</th>
<th>P-value interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Both chronic bronchitis and frequent exacerbations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.65 (0.19–2.28)</td>
<td>0.502</td>
<td>3.86 (1.31–11.4)</td>
<td>0.015</td>
<td>0.040</td>
</tr>
<tr>
<td>FEV\textsubscript{1} % pred</td>
<td>0.91 (0.86–0.96)</td>
<td>0.001</td>
<td>0.97 (0.93–1.02)</td>
<td>0.202</td>
<td>0.075</td>
</tr>
<tr>
<td>Musculoskeletal symptoms</td>
<td>2.74 (0.86–8.77)</td>
<td>0.090</td>
<td>2.45 (1.06–5.66)</td>
<td>0.036</td>
<td>0.810</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>1.19 (0.32–4.42)</td>
<td>0.798</td>
<td>1.91 (0.85–4.32)</td>
<td>0.120</td>
<td>0.275</td>
</tr>
<tr>
<td><strong>Chronic bronchitis but no frequent exacerbations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>2.47 (0.86–7.11)</td>
<td>0.095</td>
<td>4.28 (1.26–14.5)</td>
<td>0.020</td>
<td>0.339</td>
</tr>
<tr>
<td>FEV\textsubscript{1} % pred</td>
<td>1.01 (0.95–1.07)</td>
<td>0.812</td>
<td>1.01 (0.96–1.07)</td>
<td>0.741</td>
<td>0.972</td>
</tr>
<tr>
<td>Musculoskeletal symptoms</td>
<td>0.20 (0.02–1.74)</td>
<td>0.144</td>
<td>2.13 (0.78–5.80)</td>
<td>0.139</td>
<td>0.028</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>0.68 (0.13–3.68)</td>
<td>0.657</td>
<td>3.25 (1.23–8.64)</td>
<td>0.018</td>
<td>0.474</td>
</tr>
</tbody>
</table>

**Note:** Results from multi-nominal multivariate regression analyses stratified by sex.

**Abbreviations:** OR, odds ratio; CI, confidence interval; FEV\textsubscript{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, and increased mortality, 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. Another possibility might be maintenance therapy with macrolides for reduction of exacerbation frequency. 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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