Subjects with COPD and productive cough have an increased risk for exacerbations and death

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KEYWORDS
COPD;
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Exacerbations;
mortality;
Epidemiology

Summary
Background: Chronic bronchitis is related to worse general health status, exacerbations and mortality among subjects with COPD. Also less longstanding cough and phlegm may be related to worse prognosis in COPD but this has rarely been evaluated in population-based studies.

Aim: To evaluate the relationship between productive cough, exacerbations and mortality among subjects with and without COPD.

Method: All subjects with COPD (n = 993) were identified together with sex- and age matched reference subjects without obstructive lung function impairment from four population-based cohorts in 2002–04. Baseline spirometry and structured interview including data on exacerbations last 12 months were used in this study (n = 1986) together with mortality data collected until February 2012.

Results: Productive cough was more common in COPD than non-COPD (42.8 vs. 23.5%, p < 0.001), more common in men than women, but associated to exacerbations in both sexes. COPD-subjects with productive cough had the highest risk for exacerbations in both sexes and they had a significantly increased risk for death (HR 1.48, 95% CI 1.13–1.94) also when adjusted for sex, age, BMI, smoking habits and heart disease.

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Conclusion: Productive cough was common and increased the risk for exacerbations in both sexes, in both COPD and non-COPD. COPD-subjects with productive cough had the highest risk for exacerbations and a significantly higher risk for death also after adjustment for common risk factors. © 2014 Elsevier Ltd. All rights reserved.

Background

It has been clearly established during recent years that COPD is not a single disease but a heterogeneous syndrome including systemic effects. Different phenotypes have been described [1,2], even though there are yet no generally accepted classifications of phenotypes. Among phenotypes based on clinical data the bronchitis phenotype deserves special attention. Already in 1986 an increased mortality was described among male workers with chronic phlegm [3], supported also by later studies [4,5]. According to a recent review the prevalence of chronic bronchitis among subject with COPD is in the wide range of 14—74% [6], while a pooled prevalence of chronic bronchitis, regardless of COPD, was estimated at 7.6% [7]. As COPD [8,9], also chronic bronchitis seems to be an under-diagnosed condition [7,10]. Presence of chronic bronchitis among subjects with COPD is associated with worse lung function, worse general health status, more exacerbations [6,11] and increased mortality [4–6] when compared to those without chronic bronchitis.

Productive cough without fulfilling the two years interval included in the definition of chronic bronchitis is also common, and was reported by every third subject in the Lung Health Study where only smokers with mild-to moderate COPD were included [12]. This less long-standing symptom was likewise related to worse outcome such as accelerated lung function decline and increased mortality. It is important to find simple tools, such as clinical characteristics, sensitive enough to early detect signs that are of prognostic value in COPD. However, population-based data are scarce and possible sex differences regarding prevalence and prognostic impact of less long-standing bronchitis symptoms such as productive cough have hardly been evaluated even though it is known that women are more vulnerable to tobacco smoke increasing the risk for COPD [13].

Within the epidemiological research programme OLIN (Obstructive Lung Disease in Northern Sweden) studies, a population-based cohort comprising subjects with and without obstructive lung function impairment is followed longitudinally [14]. The aim of this study was to evaluate the impact of productive cough on exacerbations and mortality among subjects with and without COPD. A further objective was to evaluate possible sex differences.

Material & methods

The study population constituting the OLIN COPD study was recruited from four adult population-based cohorts examined during 2002–2004. The recruitment process has been presented previously [14]. The study population included 1986 subjects; 993 with COPD and 993 age- and sex matched subjects without obstructive lung function impairment. In the current study cross-sectional data from structured interview and spirometry performed during examinations in 2002–04 were used. Mortality data was collected from the national mortality register from the date of examination at recruitment until February 2012, corresponding to a follow-up time in the range of eight to ten years. The study was approved by the Regional Ethics Committee at Umeå University.

Structured interview

Previously well-validated questions regarding respiratory symptoms were included in the interview questionnaire [5,8,15]. Productive cough was defined as affirmative answer to the question ‘have you had cough with phlegm most days during at least three months during the last 12 months?’. Exacerbation was defined as affirmative answer to the question: ‘have you contacted health care due to respiratory complaints during the last 12 months?’ Exacerbations were classified as ‘any exacerbation during the last 12 months’ and ‘frequent exacerbations’ defined as two or more such events during the last 12 months. Smoking habits were classified into the following groups: non-smokers, ex-smokers (stopped at least one year before the baseline visit) and current smokers. The variable ‘heart disease’ included self-reported angina pectoris, previous coronary artery bypass surgery, previous percutaneous coronary intervention, myocardial infarction or heart failure.

Spirometry and classification of COPD

The lung function tests were performed using a dry spirometer, Mijnhardt Vicastet 5 by following the ATS, American Thoracic Societies, guidelines [16]. COPD was defined as FEV1/best of VC or FVC < 0.70. Classification of disease severity was made according to the GOLD, Global initiative of Obstructive Lung Disease, spirometric criteria into grade 1–4, based on FEV1 percent of predicted [17]. Swedish reference values were used [18].

Statistical analysis

Statistical calculations were made using the Statistical Package for the Social Sciences (SPSS) software version 19.0. A p-value of < 0.05 was regarded as statistically significant. The chi-squared test was used for bi-variate comparisons and to test for trends. The number of missing answers was all through low, and did not exceed 1%. Due to a low number of
subjects GOLD grades 3–4 were grouped together in the analyses. Crude mortality was based on data collected from baseline at recruitment in 2002–2004 until February 2012. Risk factors for exacerbations were calculated in a multivariate regression model including the co-variates sex, age, BMI, smoking habits, heart disease and non-COPD and COPD with respectively without productive cough. Separate analyses were also performed by sex. Survival over time of subjects with and without COPD with respectively without productive cough is illustrated by a Kaplan Meier curve. Non-COPD and COPD with respectively without productive cough was analysed as risk factors for death expressed as Hazard Ratio (HR) using 95% confidence intervals (CI) for statistical significance in a Cox regression model including the co-variates sex, age, BMI, smoking habits and heart disease. Similar analyses were also performed stratified by sex.

**Results**

**Baseline characteristics**

Productive cough and exacerbations during the last 12 months were significantly more common in COPD compared to non-COPD (42.8 vs. 23.5%, \( p < 0.001 \) and 20.7 vs. 9.0%, \( p < 0.001 \)). There was no significant difference regarding heart disease when comparing COPD and non-COPD, 18.6% and 16.1% (\( p = 0.139 \)). Productive cough was more common in men than women, significantly so in COPD, but without reaching statistical significance in non-COPD (Table 1).

**Subjects with and without productive cough**

Subjects with productive cough were older compared to those without in both COPD and non-COPD. ‘Any exacerbation’ was significantly more common among subjects with productive cough in both COPD and non-COPD (Table 2). This pattern was similar in men and women (Fig. 1).

**Risk factors for exacerbations**

In a multivariate model adjusting for sex, smoking habits, age, BMI, and heart disease there was an increased risk for ‘any exacerbation’ in non-COPD with productive cough (OR 4.13, 95% CI 2.61–6.54), COPD without and with productive cough (OR 2.85, 95% CI 1.92–4.23), and (OR 9.25 95% CI 6.23–13.75, respectively) when compared to non-COPD-subjects without productive cough. Analyses performed separately by sex showed similar risk factor pattern for men and women (Table 3).

**Mortality**

Mortality was significantly higher in COPD compared to non-COPD (23.3 vs. 17.6%, \( p = 0.002 \)). Men had a higher mortality compared to women in both COPD and non-COPD (Table 1). Subjects with productive cough had higher mortality compared to those without, in both COPD and non-COPD (Table 2). Survival over time in COPD and non-COPD with respectively without productive cough is illustrated by Kaplan-Meier curves (Fig. 2). Mortality was highest among COPD-subjects with productive cough, followed by non-COPD subjects with productive cough.

COPD-subjects with productive cough had significantly increased risk for death when analysed in a multivariate Cox regression model adjusting for sex, increasing age, BMI, smoking habits and heart disease (HR 1.48, 95% CI 1.13–1.94). In corresponding analyses stratified by sex, men with COPD and productive cough had significantly increased risk for death (HR 1.63, 95% CI 1.17–2.26) while the increased risk for death observed for women with COPD and productive cough did not reach statistical significance.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics, comparing men and women, among subjects with COPD and without COPD, number of subjects (percent).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>COPD</td>
</tr>
<tr>
<td></td>
<td>Men</td>
</tr>
<tr>
<td>Smoking habits</td>
<td></td>
</tr>
<tr>
<td>Non smoker</td>
<td>94(17.5)</td>
</tr>
<tr>
<td>Ex smoker</td>
<td>269(50.2)</td>
</tr>
<tr>
<td>Smoker</td>
<td>173(32.2)</td>
</tr>
<tr>
<td>Prod cough</td>
<td>260(48.0)</td>
</tr>
<tr>
<td>Exacerbations</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>108(19.9)</td>
</tr>
<tr>
<td>Frequent</td>
<td>45(8.3)</td>
</tr>
<tr>
<td>Heart disease</td>
<td>126(23.2)</td>
</tr>
<tr>
<td>GOLD grade</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>293(54.1)</td>
</tr>
<tr>
<td>2</td>
<td>211(38.9)</td>
</tr>
<tr>
<td>3–4</td>
<td>38(7.0)</td>
</tr>
</tbody>
</table>

\( A \) P-value of \(< 0.05\) was regarded as statistically significant.

\( ^a \) Comparing men and women.

\( ^b \) Two or more during the last twelve months.
Additional analyses could not demonstrate any significant interaction by sex and productive cough.

### Sensitivity analysis

Affirmative answer to the question used to define productive cough did not, per se, exclude subjects with more longstanding symptoms. Thus we made sensitivity analysis by excluding subjects with productive cough with duration two years or more. The prevalence of exacerbations was still significantly higher among subjects with productive cough, among subjects with as well as without COPD (36.6% vs. 14.5%, \(p < 0.001\) and 26.1% vs. 5.6%, \(p < 0.001\)). Productive cough was associated to significantly increased risk for exacerbations also after adjustment for sex, smoking habits and COPD, and of similar magnitude in men and women in analyses stratified for sex. The mortality was higher among subjects with productive cough compared to those without productive cough, among subjects with as well as without COPD, but without reaching statistical significance (22.0% vs. 18.3%, \(p = 0.568\) and 17.4% vs. 16.1%, \(p = 0.870\)).

Further, there was no significant difference in prevalence of exacerbations when comparing subjects with productive cough less than two years and those with productive cough with duration two years or more, in either COPD or non-COPD-subjects. Neither did corresponding analyses of mortality demonstrate any significant differences.

### Discussion

In this population-based study productive cough was related to an increased risk for exacerbations in both COPD and non-COPD. The increased risk for exacerbation was present independent of other common risk factors as smoking habits and age. COPD-subjects with productive cough had the highest risk for exacerbations, among men as well as among women. In both COPD and non-COPD, the mortality was higher in subjects with productive cough than those without, and higher in men compared to in women. Subjects with COPD and productive cough had an increased risk for death also when adjusted for known risk factors such as sex, age, BMI, smoking habits and heart disease.

Chronic bronchitis is, like COPD, an under-diagnosed condition, and only every other subject with chronic bronchitis reported a physician-diagnosis [10]. Even though tobacco smoke and age are the most well known risk factors...
for COPD and chronic bronchitis, these conditions have also been reported among non-smokers [19,20]. When evaluating the prognostic impact of bronchitis symptoms, most often the definition of chronic bronchitis, cough and phlegm on most days during three months in two successive years has been used [5,6,21,22]. Also cough and phlegm on most days during three months without requirement of two years duration was related to accelerated decline in FEV₁ decline and increased hospitalizations in the Copenhagen City heart study [23]. Productive cough, synonymous with reported ‘cough and phlegm’ was likewise related to worse outcome, i.e. increased mortality and decline in lung function among smokers with mild to moderate obstructive lung function impairment included in the Lung Health study [12]. However, it should be noted that subjects with more longstanding symptoms were not excluded in any of the two referred studies [12,23].

We have used the term productive cough, defined as cough and phlegm on most days during at least three months during the last year, similar to the definitions used in the above-referred studies [12,23]. Productive cough was common, reported by two out of five subjects with COPD, and one out of five among those without COPD, in comparison to 31% in the COPD-population of the Lung Health study [12] and around 10% in the general population sample of the Danish study [23]. We found a higher prevalence of productive cough among men than among women, and the large difference can hardly be explained by under reporting even though under reporting of bronchitis symptoms among women has been discussed in a quite recent editorial in the European Respiratory Journal [24].

The relationship between chronic bronchitis and COPD-exacerbations is well recognized [6,22], but we found that including also a shorter history of cough and phlegm, such as productive cough, was related to exacerbations not only in COPD, but also in non-COPD, and in both sexes. Among subject with productive cough, every third with COPD, and one out of five without COPD had ‘any exacerbation’, and close to every second of them was a ‘frequent exacerbator’ independent of COPD or not. Notably, COPD-subjects with productive cough had the highest risk for exacerbations in both sexes. In the PLATINO study sex differences were not evaluated, but every fifth subject with COPD and chronic bronchitis reported at least one exacerbation during the last year [21]. In the Copenhagen City Heart study, the relative risk for hospitalisation due to COPD exacerbations was increased five-fold among subjects with ‘chronic mucus hypersecretion’, and of similar magnitude in men and women [23]. Heterogeneous definition of exacerbations and definitions of bronchitis symptoms has to be taken into account when interpreting data [6,11,21,26]. For comparison to the above-referred population-based studies, the prevalence of chronic bronchitis was very high, nearly 75%, in a large but highly selected COPD-population (n = 433) recruited from pulmonary units, and more than every second of those with chronic bronchitis was a frequent exacerbator [22]. However, our population-based study show that including also less longstanding bronchitis symptoms, such as productive cough, is clinically important, increasing the risk for exacerbations defined as contact with health care due to respiratory complaints. Of importance, the sensitivity analyses strengthen our results as the increased risk for exacerbations remained in both men and women also after excluding subjects with productive cough with duration two years or more.

| Table 3 | Productive cough (prc) and COPD evaluated as risk factors for ‘any exacerbation during the last 12 months’, analyses also performed stratified by sex, in a multiple logistic regression model (OR, 95% CI). |

<table>
<thead>
<tr>
<th>‘Any exacerbation during the last 12 months’</th>
<th>All subjects</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 1986</td>
<td>N = 1084</td>
<td>N = 902</td>
</tr>
<tr>
<td></td>
<td>Or</td>
<td>95% CI</td>
<td>Or</td>
</tr>
<tr>
<td>Women</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Men</td>
<td>0.61</td>
<td>0.46–0.80</td>
<td>1</td>
</tr>
<tr>
<td>Non-COPD – prc</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Non-COPD + prc</td>
<td>4.13</td>
<td>2.61–6.54</td>
<td>4.83</td>
</tr>
<tr>
<td>COPD – prc</td>
<td>2.85</td>
<td>1.92–4.23</td>
<td>4.38</td>
</tr>
</tbody>
</table>

A P-value of <0.05 was regarded as statistically significant.

Multivariate model adjusting for age, BMI, smoking habits and heart disease.

Figure 2 Kaplan-Maiyer curves expressing survival in subjects with and without COPD, with respectively without productive cough (prc).
Table 4  Productive cough (prc) and COPD evaluated as risk factors for mortality among all subjects and stratified by sex in a multivariate Cox regression analysis, expressed as hazard ratios (HR) with 95% confidence intervals (95% CI).

<table>
<thead>
<tr>
<th>Mortality</th>
<th>All subjects</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$N = 1964^a$</td>
<td>$N = 1070$</td>
<td>$N = 894$</td>
</tr>
<tr>
<td></td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>Women</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1.56 1.25–1.94</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Non-COPD −prc</td>
<td>1</td>
<td>1.00 0.73–1.41</td>
<td>1.10 0.74–1.65</td>
</tr>
<tr>
<td>Non-COPD +prc</td>
<td>1.01 0.73–1.41</td>
<td>1.10 0.74–1.65</td>
<td>0.84 0.47–1.51</td>
</tr>
<tr>
<td>COPD −prc</td>
<td>1.08 0.83–1.42</td>
<td>1.04 0.73–1.49</td>
<td>1.15 0.76–1.74</td>
</tr>
<tr>
<td>COPD +prc</td>
<td>1.48 1.13–1.94</td>
<td>1.63 1.17–2.26</td>
<td>1.23 0.76–1.99</td>
</tr>
</tbody>
</table>

A $P$-value of $<0.05$ was regarded as statistically significant.

Overall-mortality among subjects with COPD in the population is increased [14,25] and cardiovascular comorbidity increase the risk for death [25]. In a Southern Swedish follow up of more than 22,000 middle-aged subjects, chronic bronchitis increased the risk for death among women with GOLD grade 2 and in men with GOLD grade 1 when subjects with co-morbidities as cardiovascular diseases were excluded [26]. In a 20-year follow-up of the OLIN first population based cohort chronic bronchitis as well as heart disease increased the risk for death among subjects with COPD [3]. In our study presence of productive cough affected mortality in both COPD and non-COPD; the all-cause mortality was highest among COPD-subjects with productive cough, followed by non-COPD subjects with productive cough. Subjects with COPD and productive cough had an increased risk for death also in the presence of other known risk factors for death as male gender, smoking and heart disease. In analyses stratified by sex, the increased risk for death did reach statistical significance among men but not among women. These findings do not ensure any difference between the sexes, but the results indicate that there may be sex differences; thus there is a need for further studies. Even though the statistical significance was lost, there was also a signal from the sensitivity analysis suggesting that mortality is higher in subjects with COPD and chronic productive cough than those without also after excluding those with productive cough duration two years or more. For comparison, in the previously referred studies where ‘cough and phlegm’ was associated with worse prognosis [12,23], less than two years duration of symptoms was needed to fulfill the definition of symptoms, however, it was not stated that subjects with more long standing symptoms were excluded. Phenotyping based on clinical characteristics such as presentation of symptoms is an important future research area and may give us simple and cheap tools of high prognostic value. Further studies of not only all-cause mortality but also cause of death in relation to clinical phenotypes can provide valuable information useful for risk assessment in clinical practise.

We found a high prevalence of productive cough also among non-COPD subjects, and subjects with respiratory symptoms may be over-represented in this non-COPD population. On the other hand, also a healthy survivor effect has to be taken into account, as the original cohorts from whom the study population was identified were recruited during the eighties and the nineties [14]. In this context, it has to be emphasized that productive cough may be of importance not only among subjects with COPD but also among non-COPD subjects, identifying individuals with a higher risk of developing COPD [27–29], i.e. productive cough may represent early signs of COPD. Further, non-COPD subjects with productive cough had more exacerbations compared to those without, and it has recently been shown that the burden of exacerbation-like events in important also among non-COPD subjects, negatively affecting health status and increasing health care utilization [30].

The strength of this study is the large number of subjects with COPD identified by standardized spirometry, comparable to that of the NHANES I [31], and also the PLATINO study [21]. The distribution of disease severity corresponds to what is known for the general population [8], including a majority GOLD grades 1 and 2. The sex- and age matched reference population without obstructive lung function impairment gives an excellent opportunity to evaluate the impact of productive cough comparing COPD and non-COPD. The large COPD-cohort gives statistical power enough to gain new data, such as evaluating not only the prognostic significance of a symptom as productive cough, but also to conduct analyses stratified by sex. Most often sex is treated as a confounder when estimating risk [12,21], but in this study the analyses stratified by sex allows us to consider sex-specific risk factor patterns. However, there are limitations, such as that the self-reported information about heart disease and exacerbations were not validated by medical records, and a certain recall bias cannot be excluded. Further, our definition of exacerbations did not include use of oral steroids or antibiotics, nor need for hospitalization but on the other hand, a highly clinical and health economically relevant distinction, namely symptoms that prompted contact with health care. Moreover, the observed association between productive cough and exacerbation is based on cross-sectional data, and we cannot exclude that the reported symptoms in some cases are results of an exacerbation. The spirometric criteria to
define COPD can also be discussed, and today the lower limit of normal, LLN, is recommended to define COPD in epidemiological studies [32]. However, the current study was designed shortly after the shift of the millennium when the fixed ratio, FEV₁/FVC < 0.70, was recommended to define COPD after the launch of the GOLD guidelines in 1997. It is well known that the fixed ratio will overestimate COPD among elderly, and as a consequence, GOLD 1 may include non-smokers without respiratory symptoms, especially among elderly. Still the fixed ratio is commonly used in health care, and our results can be interpreted in relation to clinical practice, even though the weaknesses of the fixed ratio always have to be taken into account.

In conclusion, in this population-based study productive cough was more common in men than in women, and associated to exacerbations in both sexes among subjects with as well as without COPD. Subjects with COPD and productive cough had the highest risk for exacerbations also after adjustment for other common risk factors, and also increased mortality. These findings imply that productive cough is a highly clinically relevant symptom; a marker of poorer prognosis in COPD that, by definition, can be identified earlier than chronic bronchitis.

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References


Subjects with COPD and productive cough


