Predictors of lung function and its decline in mild to moderate COPD in association with gender: Results from the Euroscop study


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Summary

Background: There is increasing appreciation of gender differences in COPD but scant data whether risk factors for low lung function differ in men and women. We analysed data from 3 years follow-up in 178 women and 464 men with COPD, participants in the Euroscop Study who were smokers unexposed to inhaled corticosteroids.

Methods: Explanatory variables of gender, age, starting age and pack-years smoking, respiratory symptoms, FEV1%FVC and FEV1%IVC (clinically important measures of airway obstruction), body mass index (BMI), and change in smoking were included in multiple linear regression models with baseline and change in post-bronchodilator FEV1 as dependent variables.

Results: Reduced baseline FEV1 was associated with respiratory symptoms in men only. Annual decline in FEV1 was not associated with respiratory symptoms in either men or women, and was 55 ml less in obese men (BMI $\geq$ 30 kg/m²) than men having normal BMI, an effect not seen in women. It was 32 ml faster in women with...
FEV1%FVC < median than women with less airway obstruction, a larger difference than in men (8 ml per year). It was 17.7 ml/year faster when increasing the daily number of cigarettes by 10 in men only, but not significantly greater than in women. Conclusion: Respiratory symptoms were associated with reduced baseline FEV1 in men with COPD. In men, obesity was associated with reduced decline and increasing the number of cigarettes smoked with increased decline in lung function. In women more severe airway obstruction was associated with accelerated decline.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a worldwide major cause of morbidity and mortality. Cigarette smoking is the principal cause of reduced lung function, the prime characteristic of COPD.1,2 Other factors associated with reduced lung function and/or accelerated lung function decline in the general population are gender, body weight, and respiratory symptoms.3-6

The prevalence of COPD is higher in men than women, which is generally attributed to higher historical rates of cigarette smoking in men. However, some studies suggest that women are more susceptible to the deleterious effects of cigarette smoke, which may partly contribute to an observed recent increase in female prevalence rates of COPD.7-10 Burrows et al.11 suggested that a low initial level of lung function would predict subsequent rapid decline in FEV1 in smokers, the so-called “horse racing effect” a phenomenon they found only in men. There are only a few longitudinal analyses available which assess gender differences in the susceptibility to cigarette smoke and subsequent change in lung functions. The results of these studies are not consistent12,13 and given the use of different statistical and design methodologies they are hard to compare. Thus, further longitudinal research is required regarding a possible difference in gender susceptibility to the harmful effects of smoking.

The Lung Health Study assessed effects of changes in smoking habits on lung function decline in established COPD. Women who became sustained quitters had an average improvement in FEV1% predicted during the first year that was 2.5 times as great as the improvement in men.14 Respiratory symptoms like chronic cough and chronic mucus hyper secretion have also been associated with accelerated decline in lung function15 and increased mortality rates in COPD.16 However, whether this association differs between men and women is not clear. Furthermore, excess weight gain has been associated with reduction in lung function, particularly FVC. The effect was larger in men,5 possibly due to a central pattern of fat distribution in men compared with women.17 Given the paucity of longitudinal data regarding possible gender differences in predictors of lung function and its decline in subjects with COPD, we evaluated smokers with mild to moderate COPD who received placebo medication during the Euroscop study, previously published.18

Methods

Subjects

The design of the Euroscop study has been published elsewhere.18 In brief, 39 study centres in nine European countries participated in a randomised double-blind, placebo-controlled study testing twice-daily treatment with 400 µg budesonide (via Turbuhaler) versus placebo. This study uses patients from the placebo arm only, as we wished to study the risk factors associated with decline in lung function that occurs naturally without any possible influence from inhaled corticosteroid. Persons were aged 30-65 years with a smoking history of at least five pack-years with a post-bronchodilator FEV1 between 50% and 100% predicted and the ratio of pre-bronchodilator FEV1 to slow inspiratory vital capacity (IVC) less than 70% predicted. Increase in FEV1 after inhalation of 1 mg terbutaline had to be <10% of normal predicted value. Patients with a history of asthma, allergic rhinitis or who had used oral glucocorticosteroids for more than six months prior to study entry were excluded.

Clinic visits and spirometry

Baseline data regarding height, weight, smoking and smoking history were recorded. Subjects were seen every three months for spirometry and were followed for three years. Each centre was supplied with a dry rolling-seal spirometer and the criteria of the American Thoracic Society were used to determine FEV1.19 The spirometry process has been stated elsewhere,18 the largest values for IVC and
FEV₁ were accepted from three manoeuvres, provided the second largest measure was within 0.1 L or 5% of the largest. FEV₁ was obtained 15 min after the inhalation of 1 mg terbutaline. Information regarding smoking habit was collected at each three monthly visit and symptom assessment was performed at baseline and annually thereafter at 12, 24 and 36 months. The Phadiatop test was used to detect specific IgE antibodies to a panel of common inhalant allergens (Pharmacia Upjohn, Uppsala, Sweden).

**Statistical analysis**

Analyses were performed to measure the association of each explanatory variable with level of post-bronchodilator FEV₁ at baseline and subsequent annual decline in post-bronchodilator FEV₁. Explanatory variables included BMI, calculated as weight (kilograms) divided by height (metres²) and divided into categories: underweight ≥ 18.5 kg/m²; normal weight = 18.5–24.9 kg/m²; overweight = 25.0–29.9 kg/m²; obese ≥ 30 kg/m². The normal weight range was the reference category. Other explanatory variables included gender, age, height, age at starting to smoke, FEV₁%FVC (dichotomised into subjects above and below the median—women 64.5% and men 63.3%, respectively), FEV₁%IVC (dichotomised into subjects above and below the median, women 65.5% and men 63.7%, respectively), specific IgE, pack-years of smoking, and change in smoking habit (individual regression lines of the number of cigarettes smoked per day against time as a predictor for annual change in FEV₁ only). Current number of cigarettes smoked was not included in the models as it has high co-linearity with pack-years and additionally is not applicable to all participants as some patients may have stopped smoking at times during the study, although all patients were smokers at baseline.

Level of reversibility was not included as it was an inclusion criterion and by definition had to be below 10%. Phadiatop was tested in all models, but the association with FEV₁ at baseline or over time lacked significance. To limit the loss of degrees of freedom it was subsequently removed from analyses. The following respiratory symptoms at baseline were tested separately in the models (adjusted for age, height, pack-years smoking, age at starting to smoke and BMI) to avoid co-linearity: wheeze at any time, waking with chest tightness, dyspnea at rest, dyspnea after activity, woken by dyspnea, woken by coughing, morning cough or phlegm in winter, cough or phlegm anytime in winter and chronic mucous hyper secretion (defined as having both cough and phlegm for 3 months or more in the last year). Estimates plus 95% confidence intervals (CI) describe the association between each explanatory variable and the two outcome variables: baseline FEV₁ and decline in FEV₁. Multiple regression analyses for baseline FEV₁ were performed using ordinary least squares (OLS). Linear mixed effects models (LMEs) can be used for longitudinal analysis to assess differences in the effect of a risk factor over time between men and women for change in FEV₁, but requires use of a three way interaction term between time, the risk factor and gender. To simplify the presentation, OLS could be used on the individual regression slopes (unweighted individual regression lines of the FEV₁ against time), but outliers in the data can distort the findings. Therefore, we opted to use robust MM regression on these individual regression slopes in S-Plus (version 6.1), due to the minimal influence caused by outlying data using this method. The robust regression method uses the MM-estimate computational strategy proposed by Yohai, Stahel and Zamar (1991), and supported by a number of robustness experts who participated in the 1989 IMA summer conference on “Directions in Robust Statistics and Diagnostics.” To test for the effect of each risk factor separately in men and women, models incorporating gender interaction terms with each explanatory variable were performed. Alpha was set at 0.05.

**Results**

Table 1 shows the baseline characteristics of 642 out of the original 643 patients (178 women) who were randomly assigned to the placebo arm of the study. One patient was removed from the original placebo group who was an extreme outlier with 86 pack-years of smoking but still exhibited a 148 ml per year lung function improvement. This one patient’s values disproportionately affected the pack year co-efficient and as her lung function improvements were counter to that expected in such a heavy smoker, it was decided to exclude her from analyses. Men were taller, with a larger weight and BMI and had a higher prevalence of atopy than women. All participants exhibited poorly reversible airflow limitation and women and men showed similar median post-bronchodilator FEV₁% predicted values (81.5% and 79.2% respectively). The prevalence of symptoms was similar between men and women, except for phlegm day or night in winter, which had a significantly higher prevalence in men than in
women (45% versus 35%, respectively). Woken by an
attack of coughing had a lower prevalence in men
than in women (35% versus 56%) as did cough during
the day or night in winter (49% versus 58%). Women
started to smoke at a significantly later age than
men (median 17 versus 15 years) and had a
significantly lower number of pack-years of smoking
(29.5 versus 38.3). All participants had decreased
their daily cigarette consumption during the 6
months prior to randomisation to a median of
16.0 for women and 20.5 for men Of the 642 study
participants, 349 patients continued smoking
throughout the 3 year follow up period. (104 out
of 178 females and 245 out of 464 males). There
was no significant difference over the study period
in the proportions of males and females who
continued to smoke. Only 5 patients (all male) quit
after the baseline visit and sustained quitting
throughout the study. A further 29 (90% male)
patients quit during the study and sustained
quitting for 4 or more visits (1 year) and did not
return to smoking. The remaining patients tried
quitting at various times but always returned to
smoking.

Risk factors for baseline level of FEV1

Table 2 illustrates the cross-sectional multiple
regression analysis assessing risk factors associated
with level of baseline FEV1, excluding respiratory
symptoms. Only higher age and lower height were
significantly associated with lower baseline FEV1.
These associations were not different for men and
women.

Risk factors for change in FEV1 over time
using robust regression

Table 4 shows the results for annual change in FEV1.
Men with a BMI $\geq 30$ kg/m² had a significantly lower
decline in FEV1 (55 ml per year) compared to men

Table 1 Baseline characteristics of females and males.

<table>
<thead>
<tr>
<th></th>
<th>Females = 178</th>
<th>Males = 464</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>52.0 (46.0–58.0)</td>
<td>54.0 (48.0–58.0)</td>
<td>0.117</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.0 (160.0–169.0)</td>
<td>176.0 (172.0–180.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.0 (55.0–70.0)</td>
<td>78.0 (70.0–85.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.9 (20.5–25.3)</td>
<td>24.7 (22.7–27.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age start smoking (year)</td>
<td>17.0 (15.0–20.0)</td>
<td>15.0 (14.0–18.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pack years of smoking (year)</td>
<td>29.5 (21.0–40.0)</td>
<td>38.3 (28.5–51.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of cigarettes/day</td>
<td>16.0 (10.0–22.8)</td>
<td>20.5 (10.0–22.0)</td>
<td>0.829</td>
</tr>
<tr>
<td>FEV1 (l)*</td>
<td>2.1 (1.7–2.4)</td>
<td>2.8 (2.3–3.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV1%predicted*</td>
<td>81.5 (70.6–89.4)</td>
<td>79.2 (68.8–88.3)</td>
<td>0.279</td>
</tr>
<tr>
<td>FEV1%IVC*</td>
<td>64.5 (59.1–67.9)</td>
<td>63.3 (57.1–66.9)</td>
<td>0.024</td>
</tr>
<tr>
<td>FEV1%FVC*</td>
<td>65.5 (59.8–69.8)</td>
<td>63.7 (58.0–68.4)</td>
<td>0.022</td>
</tr>
<tr>
<td>Reversibility % predicted</td>
<td>2.9 (0.0–5.7)</td>
<td>2.7 (0.0–5.1)</td>
<td>0.551</td>
</tr>
<tr>
<td>Phadiatop, % positive</td>
<td>9.1</td>
<td>22.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wheezing at anytime %</td>
<td>60.5</td>
<td>54.1</td>
<td>0.147</td>
</tr>
<tr>
<td>Woken with chest tightness%</td>
<td>13.1</td>
<td>11.7</td>
<td>0.630</td>
</tr>
<tr>
<td>Attack of dyspnea at rest%</td>
<td>6.2</td>
<td>6.9</td>
<td>0.745</td>
</tr>
<tr>
<td>Attack of dyspnea after activity%</td>
<td>39.9</td>
<td>34.6</td>
<td>0.215</td>
</tr>
<tr>
<td>Woken by attack of dyspnea %</td>
<td>4.5</td>
<td>4.3</td>
<td>0.919</td>
</tr>
<tr>
<td>Woken by an attack of coughing %</td>
<td>55.9</td>
<td>34.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cough in morning in winter %</td>
<td>54.5</td>
<td>53.4</td>
<td>0.812</td>
</tr>
<tr>
<td>Cough day/night in winter %</td>
<td>58.4</td>
<td>48.7</td>
<td>0.027</td>
</tr>
<tr>
<td>Phlegm in morning in winter %</td>
<td>41.8</td>
<td>50.4</td>
<td>0.051</td>
</tr>
<tr>
<td>Phlegm day/night in winter %</td>
<td>34.8</td>
<td>44.7</td>
<td>0.023</td>
</tr>
<tr>
<td>Chronic mucus hypersecretion %</td>
<td>26.6</td>
<td>28.1</td>
<td>0.691</td>
</tr>
</tbody>
</table>

*Respiratory function tests performed after dilation with 1 mg terbutaline except FEV1%IVC which was performed prior to
dilation.
of normal BMI range (18.5–24.9 kg/m²). This effect was significantly different to women, who did not exhibit this phenomenon.

The FEV₁/FVC > median level at baseline was significantly associated with change in FEV₁ over time in women who exhibited 31.3 ml per year reduced decline than females below the median FEV₁/FVC. This was not seen in men. This observed difference between men and women did not reach statistical significance using a gender interaction term in the model. Figure 1 illustrates the association between FEV₁/FVC and annual change in FEV₁. If FEV₁/FVC was substituted in the model, there was a trend in the same direction with regard to change in FEV₁ for women (RR 25.5, 95% CI 1.0–52.0) but not for men (RR 12.9 95% CI –3.8–29.5).

An increase in the number of cigarettes smoked by 10 per day during each yearly interval was associated with a trend in the same direction with regard to change in FEV₁. If FEV₁/FVC was substituted in the model, there was a trend in the same direction with regard to change in FEV₁ for women (RR 47.7, 95% CI 1.2–366.4) but not for men (RR 7.7, 95% CI 1.4–23.4).
Pack-years of smoking, age and age at starting to smoke were not associated with annual change in FEV1. Respiratory symptoms were tested separately in the main model and none of them were significantly associated with annual change in FEV1 (results not shown).

Discussion

This study shows that there are some gender differences in risk factors for both baseline level and annual change of lung function in COPD patients with current mild to moderately severe airflow limitation and a significant smoking history. A striking observation is that for all respiratory symptoms reported, except attacks of dyspnea at rest, men had a reduced FEV1, an effect not seen in women. Furthermore, men with a BMI ≥ 0 kg/m² had a 55 ml reduction in their annual decline in FEV1 compared to men with BMI in the normal range, an effect again not observed in women. Women with less airway obstruction (FEV1/FVC above the median) had a 32-ml per year reduced decline in lung function compared to women with more severe airway obstruction women, a larger difference than that seen in men (8 ml). Increasing the number of cigarette smoked by 10 per day was significantly associated with a steeper decline in men only, although the difference between men and women was not significant. Pack-years of smoking and age at starting to smoke surprisingly were not associated with either baseline FEV1 or its subsequent decline.

Respiratory symptoms and FEV1

Respiratory symptoms generally occurred with a similar prevalence in men and women, varying from 6 up to 61% depending on the type of symptoms, but presence of these symptoms was only significantly associated with a lower level of lung function in men. We believe this is the first time that such a gender effect has been observed in individuals with established COPD. The Lung Health Study reported a trend of a somewhat higher prevalence of symptoms in men, which they explained by an added contribution of occupational exposures from dusts and fumes in men and not in women.21 Our results in individuals with established irreversible airflow limitation support

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Multiple linear regression (RR) for predictors of annual change in FEV1.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Females</td>
</tr>
<tr>
<td>Age (year)</td>
<td>0.19 (−1.84–2.21)</td>
</tr>
<tr>
<td>FEV1/FVC (&gt; median)</td>
<td>31.33 (4.58–58.09)*</td>
</tr>
<tr>
<td>Pack years (year)</td>
<td>−0.12 (−1.20–0.97)</td>
</tr>
<tr>
<td>Age start smoking (year)</td>
<td>−0.83 (−4.81–3.15)</td>
</tr>
<tr>
<td>ΔCigarettes smoked (10 c/year)</td>
<td>1.35 (−42.00–44.7)</td>
</tr>
<tr>
<td>BMI 16–18.5 (kg/m²)</td>
<td>11.23 (−43.1–65.66)</td>
</tr>
<tr>
<td>BMI 25–29.9 (kg/m²)</td>
<td>−2.22 (−32.96–28.51)</td>
</tr>
<tr>
<td>BMI ≥ 30 (kg/m²)</td>
<td>−19.57 (−76.59–37.44)</td>
</tr>
</tbody>
</table>

*Estimate is significant at 0.05.
†Compared to BMI 18.5–24.9 (normal range).
‡Change in cigarettes: increase or decrease of ten per day during the yearly interval.

Figure 1 Decline in lung function over 36 months for males and females.
previous data reporting lower levels of lung function in symptomatic individuals from general populations\textsuperscript{4,13,22} Furthermore, some of these studies have also reported that this association was present in men but not women.\textsuperscript{4,13} Whether these symptoms are markers of alteration in the airways is not clear, as the precise pathogenic mechanisms underlying symptoms such as chronic phlegm production are not yet known.

We did not find any association between symptoms and lung function decline for either men or women. Thus, despite a gender difference in the cross-sectional relationship of symptoms with baseline FEV\textsubscript{1} no effect on the subsequent course in FEV\textsubscript{1} was observed. One study reported findings for men and women similar to ours\textsuperscript{14} whilst another found that individuals with wheeze had a less steep decline.\textsuperscript{23} However, many of the latter patients who had severe airflow limitation also had significant reversibility. Thus it may well be that the reported association reflected the inclusion of asthmatics in that particular study.

\textbf{FEV\textsubscript{1}}%FVC, FEV\textsubscript{1}%IVC and annual change in \textbf{FEV\textsubscript{1}}

Our findings show that, after adjusting for pack-years of smoking, change in number of cigarettes smoked and age at starting to smoke, women with mild airway obstruction, assessed by FEV\textsubscript{1}%FVC showed a significantly smaller decline in FEV\textsubscript{1} than women with more severe airway obstruction. Men did not exhibit this difference. When airway obstruction was measured by FEV\textsubscript{1}%IVC we found a similar trend of a greater difference in decline in FEV\textsubscript{1} between women according to level of airway obstruction but this effect was again not seen in men. Connett et al.\textsuperscript{24} reported that in the Lung Health Study sustained quitters of smoking gained more in FEV\textsubscript{1}% predicted and women made 2.5 times better gain than men. It is possible that our results could be influenced by smoking cessation differences between men and women, as more men were observed to quit than women. We therefore examined whether the number of quitters by level of airway obstruction differed between men and women in our study, which was not the case. Hence quitting smoking is not likely an explanation for our observation. Additionally, the inclusion of \textsuperscript{24}cigarettes smoked (a change of 10 cigarettes per day during the yearly interval) in our models partly adjusts for any putative changes in exposure to cigarettes. The number of sustained quitters in this population is also very small which makes any significant association between quitting and lung function hard to assess.

\textbf{Smoking and FEV\textsubscript{1}}

Anthonisen et al.\textsuperscript{25} concluded in a study of the 77.4% surviving participants of the Lung Health Study that lung function loss is similar between sexes in patients who continue to smoke and our findings support this. However, we show that an increase in the number of cigarettes smoked resulted in a steeper FEV\textsubscript{1} decline in men but not significantly more so than in women. It is not fully clear why this would be, given the general held increased susceptibility to smoking of women. One simple explanation might be the lower number of women under study, hence some lack of power. It is surprising that pack-years smoking or age at starting to smoke did not detrimentally affect lung function. However, this Euroscop population had by definition mild to moderate disease and these findings may not apply in a more severe population where pack years might show a stronger association. Wang et al. showed that pack-years smoking was a significant predictor of reduced maximal level of FEV\textsubscript{1} in men but not women between the ages of 15 and 35.\textsuperscript{26} Thus it may well be that the damage caused by cumulative smoke exposure happens early in men, preventing attainment of maximum lung function but does not necessarily contribute to later decrements, which in men appears to be more affected by amount of current exposure.

\textbf{BMI and FEV\textsubscript{1}}

Having a BMI $\geq 30$ kg/m$^2$ was positively associated with the annual change in FEV\textsubscript{1} in men only i.e. lung function improved or declined less rapidly in obese male subjects. Obesity is generally associated with reduced FEV\textsubscript{1} and weight gain has been shown longitudinally to reduce pulmonary function\textsuperscript{3,5} Men in particular are prone to this problem due to a central pattern of fat distribution that appears to be age related, being of greater risk prior to 60 years.\textsuperscript{17,27} However, BMI as a marker of adiposity cannot differentiate between muscle tissue and body fat which might affect lung function, but this study was not designed to assess these outcomes and no data is available regarding these physical measurements. Additionally the study did not assess weight measurements through time so it is not possible to assess how changes in weight may have impacted upon the reduced decline in lung
function when compared to normal weight individuals.

In summary, we found gender differences related to predictors of FEV₁ and its subsequent decline in a population of men and women smokers with mild to moderate airway obstruction. Respiratory symptoms were associated with reduced baseline FEV₁ in men but not women. In men only, FEV₁ loss over time was less with high BMI levels. In women annual change in FEV₁ was associated with the level of airway obstruction, an effect not seen in men. Finally increasing the amount of cigarettes smoked caused a steeper decline in FEV₁ in men.

Acknowledgements

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Reference