Hospital admission rates among men and women with symptoms of chronic bronchitis and airflow limitation corresponding to the GOLD stages of chronic obstructive pulmonary disease—A population-based study

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KEYWORDS
Cardiovascular; COPD; Epidemiology; GOLD stages; Hospitalisation; Symptoms of chronic bronchitis

Summary
Chronic obstructive pulmonary disease is a major cause of increased morbidity and mortality. The aim of this study was to investigate hospital admission rates among individuals with symptoms of chronic bronchitis and among those with airflow limitation corresponding to GOLD stages 1–4.

Method: Between 1974 and 1992, 22 044 middle-aged individuals participated in a health screening, which included spirometry (without broncho-dilation), as well as recording of respiratory symptoms and smoking habits. Information on hospital admissions until 31 December 2002 was obtained from local and national registers. The hospital admission rates due to all causes, obstructive lung disease and cardiovascular disease were analysed among individuals with symptoms of chronic bronchitis and among those with airflow limitation corresponding to GOLD stages 1–4 using ordinal regression with adjustment for age and with individuals with normal lung function and without symptoms of chronic bronchitis as reference group.

Results: Symptoms of chronic bronchitis and GOLD stages 1–4 showed increased hospital admission rates (hospital admission rates due to obstructive lung disease excluded) among smokers of both genders. Furthermore, symptoms of chronic bronchitis showed increased hospital admission rates due to obstructive lung disease among smoking women. There were also increased hospital admission rates due to obstructive lung disease among
Background

Chronic obstructive pulmonary disease (COPD) is a leading cause of increased morbidity and mortality.\(^1\) It is estimated that COPD ranks fifth as a worldwide burden of disease by 2020.\(^2\) With the aim of increasing awareness of COPD and decreasing morbidity and mortality from the disease, the Global Initiative for Chronic Obstructive Lung Diseases (GOLD) guidelines were published in 2001\(^3\) thereafter revised 2003, 2004, 2005 and 2006.\(^3\) According to GOLD, COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response to noxious particles and gases.\(^4\) The early development and progression of COPD is yet not clarified and many questions remain.\(^4\) An at-risk stage GOLD stage 0 (chronic cough and sputum production, normal spirometry) was introduced in 2001 in the GOLD classification of COPD. The relevance of symptoms of chronic bronchitis and thus of GOLD stage 0 as a risk factor for COPD development has been debated.\(^5\) It has been recognised that some smokers may develop COPD without having symptoms of chronic bronchitis in the early stages of the disease whereas other smokers with symptoms of chronic bronchitis may not develop COPD at all.\(^3\),\(^6\) Due to incomplete evidence that individuals who meet the definition of stage 0 necessarily progress to stage 1, mild COPD, the stage 0 that appeared in previous classifications is no longer included as a stage of COPD.\(^3\) However, the current GOLD guidelines underline that chronic cough and sputum production are not normal and the underlying cause should be searched for.\(^3\) Although thus perhaps not associated with COPD development, symptoms of chronic bronchitis could nevertheless be of importance with respect to long-term morbidity in affected individuals. These aspects are not very well studied despite the fact that the disorder is very common, especially among smokers.

In established COPD an important aspect of morbidity are the periods of worsening of the disease, exacerbations, which are common and place a burden on the patient\(^7\) and health services.\(^8\) An exacerbation may require physician consultation in primary or secondary care, and may result in a hospital admission and even lead to death.\(^8\) Furthermore it is recognised from epidemiological studies that individuals with reduced lung function have an increased risk of cardiovascular disease independent of smoking.\(^9\) In some previous studies, co-morbid conditions such as cardiopulmonary disorders and respiratory cancer were more common among patients with COPD. Furthermore, patients with COPD also showed higher risks of hospital admissions and death due to cardiovascular disease.\(^10\),\(^11\) There are, however, few population-based studies on the influence of COPD on subsequent long-term morbidity. COPD is often under-diagnosed\(^12\) and such studies could also encompass the morbidity among individuals with airflow limitation but without a known COPD diagnosis.

The aims of this study were to investigate the total, obstructive lung disease and cardiovascular morbidity as reflected in hospital admission rates among individuals with symptoms of chronic bronchitis and among those with airflow limitation corresponding to GOLD stages 1–4.

Study population and methods

The Malmö Preventive project

With a population of 250,000 inhabitants, Malmö is Sweden’s third largest city. The Malmö Preventive programme (MPP), a preventive, case-finding programme for cardiovascular risk factors and alcohol abuse was created in 1974 at the Department of Preventive Medicine of Malmö University Hospital. The aim of this programme was to screen large strata of the adult population, mostly middle-aged men and women born in pre-specified years, in order to find high-risk individuals for preventive intervention.\(^14\),\(^15\) All individuals who participated in the MPP took part in a comprehensive health screening, which included a physical examination, spirometry and blood tests. Additionally, lifestyle-related risk factors were assessed by means of a self-administered questionnaire including questions on smoking habits. The questions regarding smoking habits and tobacco consumption varied during the screening period and thus between cohorts. Some cohorts did not receive a detailed questionnaire regarding tobacco consumption and some cohorts did not perform a spirometry. Various interventions (lifestyle modification, drug therapy) were offered to nearly 25% of the screened individuals for shorter or longer periods.\(^14\),\(^16\) Intervention against smoking was, however, only instituted if another cardiovascular risk factor was present and consisted of advice given by a nurse to stop smoking, sometimes supported by the measurements of carboxy-haemoglobin (COHb) and feedback information to the individual with a history of smoking.\(^17\)

Study population

Between 1974–1992 whole age-cohorts were invited to the programme with an overall attendance rate of 70 percent (range 64–78) resulting in a total of 33,346 screened...
individuals, 22,444 men (mean age 44 years range 27–61) and 10,902 women (mean age 50 years, range 28–58). The present study was based 22,044 individuals 14,630 men and 7,414 women from with detailed information regarding their tobacco consumption and who had also performed lung function tests. The study population and exclusions have been described in a previous study and in a flow-chart of the study population (Figure 1).

Assessment of smoking habits

Tobacco smoking is a well-known risk factor for COPD development. People who have never smoked with respiratory symptoms or with signs of airflow limitation are more likely to have a diagnosis of asthma. Ex-smokers with respiratory symptoms or signs of airflow limitation constitute a heterogeneous group who might have both a diagnosis of COPD and asthma. In this study we therefore categorised the individuals according to their self-reported smoking habits into never-smokers, ex-smokers and current smokers, and all analyses were stratified accordingly. Those who gave negative answers on all smoking-related questions regarding current and previous smoking habits were classified as never-smokers. Individuals who stated that they had stopped smoking and who gave negative answers on all other smoking-related questions regarding current and previous smoking habits were classified as former smokers. Individuals who stated that they had stopped smoking and who gave negative answers on all other smoking-related questions regarding current and previous smoking habits were classified as former smokers. Individuals who stated that they were currently smoking were classified as smokers. Those who gave contradictory answers were excluded. The self-reported smoking habits have previously been validated with measurements of COHb.

Assessment of pulmonary function

Pulmonary function was assessed by a screening spirometry. A Spirotron apparatus (Drägerwerk AG, Lübeck, Germany) was used, with the individual in an upright standing position without a nose clip. Specially trained nurses performed the tests. Forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC) were recorded. One acceptable manoeuvre with respect to the individual’s cooperation and performance was required. No reversibility test was performed. FEV₁ was analysed as percentage of predicted (pred) values. Predicted values of FEV₁ were obtained from internally derived linear regressions based on height and age in a subgroup of 3,467 male and 2,961 female never-smokers.

\[
\text{Men: } \text{Pred. FEV}_1 (L) = 4.422 \times \text{height (m)} - 0.0381 \times \text{age (year)} - 2.483, \text{SD 0.63,}
\]

\[
\text{Women: } \text{Pred. FEV}_1 (L) = 3.615 \times \text{height (m)} - 0.0217 \times \text{age} - 2.134, \text{SD 0.45.}
\]

Assessment of respiratory symptoms

Respiratory symptoms were assessed by a self-administered questionnaire. Individuals who stated that they recently or previously had had episodes with chronic productive cough lasting more than 3 months, more than 2 consecutive years were regarded as having symptoms of chronic bronchitis.

Classification of pulmonary function

Symptoms of chronic bronchitis and GOLD Stages 1–4 were defined as follows:

- Symptom of chronic bronchitis: FEV₁/FVC < 0.70 and FEV₁ < 80% pred and symptoms of chronic bronchitis as defined above.
- Stage 1 (mild): FEV₁/FVC < 0.70 and FEV₁ ≥ 80% pred;
- Stage 2 (moderate): FEV₁/FVC < 0.70 and FEV₁ < 80% pred and FEV₁ ≥ 50% pred;
- Stage 3 (severe): FEV₁/FVC < 0.70 and FEV₁ < 50% pred and FEV₁ ≥ 30% pred;
- Stage 4 (very severe): FEV₁/FVC < 0.70 and FEV₁ < 30% pred.

Individuals without symptoms of chronic bronchitis and with FEV₁/FVC ≥ 0.70 and FEV₁ ≥ 80% predicted were classified as normal and used as a reference group throughout the study. Individuals who could not be classified into any of these categories were labelled as “non-classifiable”.

![Figure 1](flow-chart-of-the-study-population.png)
Register follow-up analyses

All individuals were followed in local and national registers for hospital admissions until 31st December 2002. The local patient register of Malmö started in 1974 and was completed in 1979. The Swedish Board of Health and Welfare provided data from the National Patient Registry on hospital admissions from 1987 and onwards. The register contains information regarding hospital admissions, diagnoses, date of admission, age and national identification number. Missing information regarding hospital admissions is estimated to be less than 1% per year. Information on primary diagnoses is missing in approximately 1% of the hospital admissions. In this study only hospital admissions after screening due to somatic diseases were included. Person-years when individuals were hospitalised were excluded. The vital status was unknown in 412 individuals who had left the country. The accumulated person-years until they left the country were used in the analyses. Both the primary and the secondary hospital discharge diagnoses of COPD, asthma and cardiovascular disease were used. Hospital discharge diagnoses of COPD and asthma may overlap. The term “obstructive lung disease” was therefore used, comprising both COPD and asthma. The following International Classification of Diseases (ICD) codes were used to define cause specific hospital admissions: COPD: ICD 8; 490–492 and 496, ICD 10; J40–44, asthma: ICD 8; 493, ICD 10; J45, and cardiovascular disease: ICD 8–9; 410–414, 424, 426–429, 431–444; ICD 10; I10–25, I34–37, I44–49, I50–52, I61–71.

Statistical analysis

The computer-based analysis programme, Statistical Programme for Social Sciences (SPSS) version 11.0, was used for all calculations. The number of hospital admissions per 1000 person-years due to all causes, obstructive lung disease and cardiovascular disease was calculated for each individual. Differences in hospital admission rates in GOLD stages 1–4 and in the group with symptoms of chronic bronchitis were analysed with individuals with normal lung function and without symptoms of chronic bronchitis as reference. The distribution of hospital admission rates was skewed. It was therefore necessary to use a non-parametric statistical method. Increasing age may also increase the number of hospital admissions and we regarded the adjustment for age as essential in the analyses. Ordinal regression is a relatively new statistical method which was developed for analyses of ranked outcomes. The model allows for adjustments for covariates such as age which is not possible with most non-parametrical statistical analyses. Therefore, in order to compare the hospital admission rates between the GOLD stages, the hospital admission rates were ranked and categorized and used as outcome in an ordinal regression model which also incorporated adjustment for age. All analyses were stratified for gender and smoking habits. In the analyses of hospital admission rates due to all causes, hospital admissions due to obstructive lung disease were excluded. In each of the GOLD stages, subgroups of individuals accounted for many of the hospital admissions. In some groups the majority of the individuals showed no hospital admissions at all. In order to clarify the fact that a small proportion of the individuals accounted for many events and for comparison of admission rates between groups, the 25th, 50th and 75th percentile (hospital admission rates), the 50th, 75th and 95th percentiles (hospital admission rates due to cardiovascular and obstructive lung disease) were calculated and the data presented in box-plot figures accordingly. This way of presenting the data is also in line with the non-parametric statistical method used in our analyses as described above. Several analyses were performed; some of them with statistical significance (P-value less than 0.05) may be due to chance. P-values above 0.01 should therefore be interpreted with caution.

Results

Descriptive information

The study comprised 14630 men and 7414 women in total. The mean age at baseline (years, standard deviation in brackets) in men was 46.4 (5.7) and 47.5 (7.8) in women. Among men the proportion of smokers was 49%, ex-smokers 27% and never-smokers 24%. The corresponding figures among women were 44%, 16% and 40%. Among men, the prevalence of symptoms of chronic bronchitis and GOLD stages 1–4 was 2.2%, 9.9%, 6.9%, 1.0% and 0.3%. The corresponding figures among women were 2.4%, 4.5%, 4.3%, 0.6% and 0.2%, respectively. Table 1 shows the distribution of hospital admissions by gender. About one-third of the individuals had no hospital admissions during the follow-up time. The prevalence of COPD according to age and gender is shown in Table 2. The proportions of non-classifiable individuals were 1453 (9.9%) among men and 821 (11.0%) among women. The numbers of individuals and hospital admissions in the GOLD stages are shown in Tables 3 and 4. The numbers of deaths during the follow-up time were 4365 (30%) in men and 1047 (14%) in women.

Hospital admissions due to all causes

A total of 71813 hospital admissions was recorded in the study population based on 461943 person-years (155 per 1000 person-years). Of these, the information on principal diagnosis was missing in 1388 (1.9%). A total of 22341 hospital admissions also had a secondary diagnosis. The total number of person-years excluded, because the individuals were admitted to hospital, was 1336. Among men a total of 52484 hospital admissions was recorded based on 317508 person-years (165 per 1000 person-years). Among women the number of hospital admissions was 19329 based on 144435 person-years (134 per 1000 person-years). Numbers of individuals, patients and hospital admission in the GOLD stages and among those with symptoms of chronic bronchitis is shown in Tables 3 and 4.

Hospital admissions rates in symptoms of chronic bronchitis and GOLD stages 1–4

The hospitalisation admission rates were increased among male and female smokers with symptoms of chronic bronchitis (Figure 2, Table A1 in Appendix A). The rates
Hospital admission rates with symptoms of CB and airflow limitation corresponding to the GOLD stages of COPD

were also increased in GOLD stages 1–4 among smoking men and in GOLD stages 2 and 4 among smoking women (Figure 2). Among ex-smokers and never-smokers with symptoms of chronic bronchitis and GOLD stages 1–4 there were no increased hospital admission rates.

Hospital admission due to obstructive lung disease

The total number of hospital admissions due to either COPD or asthma, both primary and secondary diagnoses (hospital admissions due to obstructive lung disease), was 2326. A total of 756 individuals in the study population were hospitalised at least once due to obstructive lung disease as defined above. There were 1067 (1.5%) of hospital admissions with COPD as the primary diagnosis and 851 with COPD as secondary diagnosis. There were 392 (0.5%) hospital admissions with asthma as the primary diagnosis and 187 with asthma as the secondary diagnosis. The hospital discharge diagnoses of COPD and asthma overlapped. Among hospital admissions with COPD as the primary diagnosis, 34 (3.2%) had asthma as a secondary diagnosis. Furthermore, of all hospital admissions with the primary diagnosis of asthma, 45 (11.5%) had COPD as a secondary diagnosis. Moreover, among a total of 386 individuals who had been hospitalised at least once with COPD as the primary diagnosis, 55 (14%) had also been hospitalised at least once with asthma as the primary diagnosis.

Hospital admission rates due to obstructive lung disease in symptoms of chronic bronchitis and GOLD stages 1–4

Increased hospital admission rates due to obstructive lung disease were found among those with symptoms of chronic bronchitis among smoking women and ex-smoking men as compared to the reference-group of individuals without symptoms of chronic bronchitis and with normal pulmonary function (Figure 3, Table A2 in Appendix A). Notably, among for instance smoking women with symptoms of chronic bronchitis, only a small subgroup (≥95th percentile) showed increased rates with 55 hospital admissions per 1000 person-years or more as compared to the 95th percentile of the reference-group which showed zero hospital admissions. The hospital admission rates also showed statistically significant increase among male and female smokers of GOLD stages 1–4. Among ex-smoking men the rates were increased in GOLD stages 1–4. No increased hospital admission rates due to obstructive lung disease was found among ex-smoking women.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Number of hospital admissions during follow-up by gender.</th>
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<tbody>
<tr>
<td>Number of hospital admissions</td>
<td>Men</td>
</tr>
<tr>
<td></td>
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<tr>
<td>0</td>
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</tr>
<tr>
<td>1</td>
<td>2604</td>
</tr>
<tr>
<td>2</td>
<td>1771</td>
</tr>
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<td>3–5</td>
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<tr>
<td>6–10</td>
<td>1974</td>
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<tr>
<td>11–15</td>
<td>676</td>
</tr>
<tr>
<td>16–20</td>
<td>246</td>
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<td>31–40</td>
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<td>23</td>
</tr>
<tr>
<td>Total</td>
<td>14630</td>
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</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Distribution of age groups and prevalence of COPD (GOLD stages 1–4) at baseline screening according to gender and age groups.</th>
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</thead>
<tbody>
<tr>
<td>Age group (years)</td>
<td>N (%)</td>
</tr>
<tr>
<td>&lt;29</td>
<td>518 (3.5)</td>
</tr>
<tr>
<td>30–34</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>35–39</td>
<td>899 (6.1)</td>
</tr>
<tr>
<td>40–44</td>
<td>2943 (20.1)</td>
</tr>
<tr>
<td>45–49</td>
<td>9043 (61.8)</td>
</tr>
<tr>
<td>50–54</td>
<td>72 (0.5)</td>
</tr>
<tr>
<td>55–59</td>
<td>547 (3.7)</td>
</tr>
<tr>
<td>Total</td>
<td>14630 (100)</td>
</tr>
</tbody>
</table>
women with symptoms of chronic bronchitis and among ex-smoking women with GOLD stages 1–4. Among never-smokers there were increased hospital admission rates due to obstructive lung disease in stage 2 among women and stages 3–4 among men.

**Hospital admissions due to cardiovascular disease**

There were a total of 17,928 hospital admissions due to cardiovascular disease either as a primary or as a secondary diagnosis. The number of individuals hospitalised due to cardiovascular disease was 5,771. The number of hospital admissions with cardiovascular diagnosis as the primary diagnosis was 15,528 and the number with cardiovascular disease as the secondary diagnosis was 6,071. Thus 3,671 hospital admissions had cardiovascular disease both as the primary and the secondary diagnoses.

**Hospital admissions due to cardiovascular disease in symptoms of chronic bronchitis and GOLD stages 1–4**

Among smoking men the hospital admission rates due to cardiovascular disease were increased in GOLD stages 2 ($P$-value 0.002) and stage 3 ($P$-value 0.02) but after adjustment for age this difference disappeared (Figure 4, Table A3 in Appendix A). Increased hospital admission rates due to cardiovascular disease were found among never-smoking men of stage 2 ($P$-value 0.004). The rates were not increased among never-smoking and ex-smoking women.

**Discussion**

This population based study of middle-aged individuals showed a substantial morbidity with increased hospital...
admission rates due to all causes and obstructive lung disease among those who smoked, with symptoms of chronic bronchitis and preserved normal pulmonary function and among those with airflow limitation corresponding to GOLD stages 1–4 as compared to the reference group of those who smoked without symptoms of chronic bronchitis and with normal pulmonary function. Furthermore, GOLD stages 2 and 4 showed an increased cardiovascular morbidity among women who smoked as compared to the reference.

In a previous study we reported an increased all-cause mortality risk associated with symptoms of chronic bronchitis. The magnitude of the risk was similar to that of GOLD stage 2. Similar findings concerning mortality among individuals with symptoms of chronic bronchitis has also
been reported previously from a study conducted in a population of working men and from the Atherosclerosis in Communities (ARIC) study. Symptoms of chronic bronchitis have been associated with an increased risk of death from pulmonary infection and have also been associated with an increased risk of death due to lung cancer. In the present study we have also found increased hospital admission rates due to all causes among individuals with symptoms of chronic bronchitis (hospital admissions due to obstructive lung disease excluded). Moreover, among female smokers with symptoms of chronic bronchitis, the hospital admission rates due to obstructive lung disease were increased as compared to the reference-group. Notably only a small subgroup (≥ the 95th percentile) in the symptomatic group of women showed increased rates. The ICD codes used in this study to define hospital admissions due to obstructive lung disease do not refer specifically to an exacerbation. However, it is reasonable to assume that these hospital admissions would be caused by an exacerbation of COPD. Our findings suggest that in contrast to some other studies, there might be a possibility that individuals with symptoms of chronic bronchitis develop significant COPD. We have no follow-up data on lung function to address this issue but findings from another Swedish study support this view.

The hospital admission rates due to all causes (excluding hospital admissions due to obstructive lung disease) were increased in GOLD stages 1–4 among smokers of both genders. Several previous studies on COPD-related morbidity have been conducted on patients with a known diagnosis of COPD, mostly based on hospital discharge diagnoses of COPD. In a study conducted in the US on a nationally representative sample, any mention of COPD in the discharge diagnosis was associated with a higher prevalence and in-hospital mortality for pneumonia, congestive heart failure, ischaemic heart disease, thoracic malignancies, and respiratory failure. In the Lung Health Study of individuals with known mild-to-moderate COPD, a total of 12.8% of participants were hospitalised with cancer, cardiovascular disease, and non-malignant respiratory disease accounting for 75% of hospital admissions. COPD is under-diagnosed also among hospitalised medical patients and COPD patients may not be identified in register-based studies. Our findings could thus provide some knowledge regarding the long-term morbidity in terms of hospital admissions due to other causes than COPD among individuals with airflow limitation.

Obstructive lung disease is frequently not listed as the underlying or contributing cause of hospitalisation. In this study, the hospital admission rates due to obstructive lung disease were increased among those who smoked with GOLD stages 1–4. This was more pronounced among subgroups of smoking women with severe COPD. In general the differences in the admission rates between groups were in the 75th–90th percentile indicating that there were subgroups of individuals within the GOLD stages 1–4 who had repeated hospital admissions due to obstructive lung disease. However, a majority of the individuals with airflow limitation showed no hospital admissions due to obstructive lung disease at all. Due to the well-known under-diagnosis of COPD, our findings probably represent an underestimation of the true hospital admission rates due to obstructive lung disease among individuals with airflow limitation.

Low FEV₁ has been associated with an increased risk of cardiovascular disease in previous studies. Register-based
and case-control studies conducted on patients with a known diagnosis of COPD from Canada and the US have shown an increased risk of hospital admission due to cardiovascular disease among individuals with COPD as compared to those without COPD.\textsuperscript{10,11,33} The hospital admission rates due to cardiovascular disease were increased among smoking women with airflow limitation (GOLD stages 2 and 4) and among never-smoking men of GOLD stage 2, which is in line with these findings.

A possible explanation for an increased all-cause mortality and morbidity among individuals with symptoms of chronic bronchitis with or without signs of airflow limitation could be an increased systemic inflammatory response.\textsuperscript{34} A systemic inflammatory response has been demonstrated among individuals with symptoms of chronic bronchitis with and without airways obstruction.\textsuperscript{34} The systemic inflammation might be the link between inflammatory lung disorders such as symptoms of chronic bronchitis and COPD, cardiovascular, other cardiorespiratory diseases and respiratory cancers.\textsuperscript{34,35}

Some methodological aspects should be pointed out. This population-based study comprised a large number of smoking men and women with information about respiratory symptoms, smoking habits and lung function measurements. Smoking habits at baseline have been validated with biochemical markers in a previous study.\textsuperscript{19} The follow-up time was substantial with a large number of hospital admissions.

A number of other possible limitations have been discussed previously.\textsuperscript{18,19} The protocol of the lung function tests did not fully meet the standards of the current recommendations.\textsuperscript{70} The values of internal regression equation based on length and age and the standard deviation of the equation was similar to that of the Working party of the European Community for Steel and Coal.\textsuperscript{16} We therefore believe that the methodological error is similar to that achieved after optimal spirometric technique. There remains a possibility of misclassification depending on reduced specificity in the spirometries, which would result in an underestimation of the results rather than the reverse. Another possible limitation is that the GOLD classification of COPD requires post-broncho-dilator values, which were not available in this study.\textsuperscript{1} In an epidemiological setting the administration of broncho-dilatation is often not feasible. The use of pre-broncho-dilator values seems to be an acceptable alternative but the results should be interpreted in this context.\textsuperscript{6} Thus, there is a possibility that individuals with asthma were included among some smokers with signs of airflow limitation. Notably, hospital admissions due to asthma were also included in the analyses due to an overlap in the hospital discharge diagnoses.

Furthermore, smoking habits were assessed at one point in time and not repeated thereafter and some smokers in this study are likely to have stopped smoking during the follow-up time\textsuperscript{27} causing a misclassification of ex-smokers as continuing smokers.

In addition, we have no follow-up data on symptoms of chronic bronchitis and thus we are not able to determine whether the symptoms of chronic bronchitis were stable or not. Symptoms of chronic bronchitis may disappear in some individuals especially in ex-smokers.\textsuperscript{5} In these individuals, symptoms of chronic bronchitis may have had a limited influence on hospital admission rates and could cause an underestimation of the effect of persistent symptoms of chronic bronchitis in this study.

Further, the local patient register started in 1974 and was amongst the first in this country to register hospital admissions. However, the register was only considered complete in 1979; thus, there is a possibility that some hospital admissions might be missed from 1974 to 1979.

Individuals not selected to this study for any reason (no spirometry, lack of data on smoking habits) showed similar distribution of socio-economic groups as compared to the selected groups in both genders. Men who were not selected were somewhat younger, (mean age 38.7 years) and perhaps healthier as compared to the selected group (46.4 years). Women who were not selected were slightly older (54.3 years) as compared to selected women (47.5 years). The prevalence of smoking was similar in both groups of men, but lower among women who were not selected, (15%), as compared to the selected women (47.5%). Finally, a potential limitation is the fact that we have no information regarding the distribution of the study interventions and thus we are not able to adjust for effects of the intervention part of the study. A previous study conducted on the MPP, birth cohorts invited to screening examination were compared to birth cohorts not invited.\textsuperscript{16} In that study, total mortality did not differ significantly between the intervention group and control group.\textsuperscript{16} Regarding the effect of non-participation, in the same study,\textsuperscript{16} non-participants showed a two-fold increased mortality risk as compared to participants.

In summary, among smokers, symptoms of chronic bronchitis and airflow limitation corresponding to GOLD stage 2–4 conveyed a substantial morbidity with increased hospital admission rates due to all causes, and due to obstructive lung disease. Airflow limitation corresponding to GOLD stages 2 and 4 increased cardiovascular morbidity among women. Hence, the burden of disease associated with symptoms of chronic bronchitis and COPD could be underestimated.

Acknowledgements

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Authors’ contributions

Marie Ekberg-Aronsson: Took part in the conception and design of the study, performed the statistical analyses and interpretation of data, drafted and revised the article, gave final approval of the version to be published.

Kerstin Löfdahl: Took part in the conception and design of the study, interpretation of data and revision of the article and gave final approval of the version to be published.

Jan-Åke Nilsson: Took part in the conception and design of the study, statistical analysis and interpretation of data and gave final approval of the version to be published.

Peter Nilsson: Took part in the conception and design of the study, acquisition and interpretation of data and gave final approval of the version to be published.

Claes-Göran Löfdahl: Took part in the conception and design of the study, acquisition and interpretation of data and revision the article, and gave final approval of the version to be published.
Competing interests
The authors have no competing interests.

Ethical approval
This study has been approved by the Swedish Data register authorities and the local Ethical committee of the Medical Faculty, University of Lund.

Appendix A

Hospital admission rates per 100 person-years in relation to symptoms of chronic bronchitis and GOLD stages 1–4 among smokers, see Tables A1–A3.

Table A1   Hospital admission rates per 100 person-years due to all causes in relation to symptoms of chronic bronchitis and GOLD stages 1–4 among smokers.*

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<tr>
<th></th>
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<td>GOLD 25th</td>
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<tr>
<td>CB</td>
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<td>166</td>
</tr>
<tr>
<td>4</td>
<td>88</td>
<td>234</td>
</tr>
</tbody>
</table>

*For comparison between symptoms of chronic bronchitis, GOLD stages 1–4 and the reference group the hospital admission rates per 1000 person-years is presented with the 25th, 50th, and 75th percentiles. The P-value represents results from ordinal regression analyses of hospital admission rates between symptoms of chronic bronchitis (CB), GOLD stages 1–4 and the reference group.
†Ref.: reference group of individuals without symptoms of chronic bronchitis and with normal pulmonary function.

Table A2   Hospital admission rates per 1000 person-years due to obstructive lung disease in relation to symptoms of chronic bronchitis and GOLD stages 1–4 among smokers.*

<table>
<thead>
<tr>
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<th>Women</th>
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<td></td>
<td>GOLD</td>
<td>COPD</td>
</tr>
<tr>
<td>Ref.†</td>
<td>97</td>
<td>15</td>
</tr>
<tr>
<td>CB</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
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<td>44</td>
<td>8</td>
</tr>
<tr>
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<td>140</td>
<td>26</td>
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<tr>
<td>3</td>
<td>128</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>7</td>
</tr>
</tbody>
</table>

COPD; numbers of hospital admissions due to COPD, asthma (primary diagnosis); numbers of hospital admissions due to asthma, OLD; hospital admissions due to both COPD and asthma (primary and secondary diagnoses).
*For comparison between symptoms of chronic bronchitis, GOLD stages 1–4 and the reference group the hospital admission rates due to obstructive lung disease per 1000 person-years is presented with the 50th, 75th, and 95th percentiles. The P-value represents results from comparison of hospital admission rates between symptoms of chronic bronchitis (CB), GOLD stages 1–4 and the reference group with ordinal regression with adjustment for age.
†Ref.: reference group of individuals without symptoms of chronic bronchitis and with normal pulmonary function.

Table A3   Hospital admission rates per 1000 person-years due to cardiovascular disease in relation to symptoms of chronic bronchitis and GOLD stages 1–4 among smokers.*

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GOLD</td>
<td>Total</td>
</tr>
<tr>
<td>Ref.†</td>
<td>4492</td>
<td>0</td>
</tr>
<tr>
<td>CB</td>
<td>232</td>
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</tr>
<tr>
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<td>1056</td>
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</tbody>
</table>
Table A3 (continued)

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<th></th>
<th>Men</th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GOLD Total</td>
<td>50th Median</td>
<td>75th perc</td>
<td>95th perc</td>
<td>P-value</td>
<td>GOLD Total</td>
<td>50th Median</td>
</tr>
<tr>
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<td>31</td>
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<td>226</td>
<td>842</td>
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</tr>
</tbody>
</table>

*For comparison between symptoms of chronic bronchitis, GOLD stages 1–4 and the reference group the hospital admission rates due to cardiovascular disease per 1000 person-years is presented with the 50th, 75th, and 95th percentiles. The P-value represents results from comparison of hospital admission rates between symptoms of chronic bronchitis (CB), GOLD stages 1–4 and the reference group with ordinal regression with adjustment for age.

†Ref.: reference group of individuals without symptoms of chronic bronchitis and with normal pulmonary function.

References

28. Lindberg A, Bjerg-Backlund A, Ronmark E, Larsson LG, Lundback B. Prevalence and underdiagnosis of COPD by disease severity and the attributable fraction of smoking report from the