Gender differences in the treatment and outcome of patients with COPD

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<tr>
<td>AHR</td>
<td>Airway hyper-responsiveness</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<td>CI</td>
<td>Confidence interval</td>
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<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>CVS</td>
<td>Cardiovascular disease</td>
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<tr>
<td>FEV1</td>
<td>Forced expiratory volume in one second</td>
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<td>FFMI</td>
<td>Fat-free mass index</td>
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<td>FVC</td>
<td>Forced vital capacity</td>
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<td>HR</td>
<td>Hazard Ratio</td>
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<td>ICS</td>
<td>Inhaled corticosteroids</td>
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<td>LTOT</td>
<td>Long-term oxygen therapy</td>
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<td>LVRS</td>
<td>Lung volume reduction surgery</td>
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<tr>
<td>OAD</td>
<td>Obstructive airways disease</td>
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<tr>
<td>PaO₂</td>
<td>Partial pressure of oxygen</td>
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Abstract

Chronic Obstructive Pulmonary Disease (COPD) is a respiratory disease characterized by progressive airflow limitation that is not fully reversible. Tobacco smoke is the most important risk factor. COPD is a leading cause of morbidity and mortality worldwide, and the burden of disease has been increasing, particularly for women.

Despite these alarming trends, little is known about gender differences in the clinical manifestations and management of patients with COPD. In a large cohort of patients with chronic airflow obstruction hospitalized for COPD, gender differences in the treatment and outcome of disease were investigated.

The cohort consisted of 19,260 women and 23,893 men with a mean age of 77 years. Women were more likely to have been previously hospitalized for asthma. In the year preceding the index hospitalization, women were dispensed fewer prescriptions for bronchodilators (particularly ipratropium bromide and theophylline) but were more likely to have received benzodiazepines and antidepressants. There were 11,245 (58.4%) female and 16,754 (70.1%) male deaths after cohort entry. The most frequent cause of death in both men and women was COPD. Mean survival and time to re-hospitalization for COPD or asthma were higher for female patients.
Résumé

La Maladie Pulmonaire Obstructive Chronique (MPOC) est une maladie respiratoire caractérisée par une augmentation de la résistance au flot respiratoire, de nature progressive et non-réversible. Le tabagisme est la principale cause de la MPOC. La MPOC est une cause importante de morbidité et de mortalité dans le monde entier, et la prévalence de la maladie continue d’augmenter de façon alarmante, tout particulièrement chez les femmes.

Malgré cet essor de la MPOC, nous en savons peu sur les différences qui peuvent exister entre les sexes, au niveau des manifestations cliniques, du traitement et de l’évolution de la maladie. Dans une cohorte de patients traités pour une maladie pulmonaire obstructive et hospitalisés avec un diagnostique principal de MPOC, nous avons comparé le traitement reçu ainsi que le pronostic de la maladie chez les hommes et les femmes.

La cohorte était constituée de 19260 femmes et 23893 hommes, et l’âge moyen était de 77 ans. Plus de femmes que d’hommes avaient été précédemment hospitalisées avec un diagnostic d’asthme. Dans l’année précédant l’hospitalisation index, les femmes avaient reçu moins de prescriptions pour des bronchodilatateurs (particulièrement le bromure d’ipratropium et la théophylline), mais plus de prescriptions pour des benzodiazépines et des antidépresseurs. Un total de 11245 (58.4%) femmes et 16754 (70.1%) hommes sont décédés après l’entrée dans la cohorte. La cause de décès la plus fréquente chez les hommes comme les femmes était la MPOC. La survie moyenne, ainsi que le temps moyen avant la ré-hospitalisation pour un diagnostic de MPOC ou d’asthme, étaient plus élevés chez les femmes de la cohorte.
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I would first like to thank my supervisors Drs. Pierre Ernst and Samy Suissa for their guidance throughout this work. I have learnt much from them regarding research methodology, critical appraisal, and scientific integrity in the face of pressures exerted by the pharmaceutical industry. I have been privileged to have two supervisors with the utmost and complementary expertise.

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I wish to thank Diane Gaudreau for secretarial assistance throughout this training – I have yet to find a question Diane cannot answer, and Stéphane for patiently dealing with my computing inadequacies. This work was supported by a fellowship from the Canadian Lung Association / Canadian Institute of Health Research and Glaxo-Smith-Kline, and I am grateful for their support.

Finally, I have to thank my parents and my sister Véronique, whose support and encouragement have never failed throughout my seemingly unending medical and research training. And I want to thank Sonny Dandona for his patience and humor in the face of both real and perceived adversity.
Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a disease characterized by progressive and mostly irreversible airflow obstruction, associated with an abnormal inflammatory response of the lungs to noxious particles or gases. Tobacco smoke is by far the most important risk factor for COPD. COPD is a leading cause of morbidity and mortality worldwide, and is expected to become the third leading cause of death by the year 2020. In particular, the burden of COPD has been increasing in women.

In recent years, mortality rates of COPD have stabilized among men, while they are still increasing among women. Similar trends of increasing COPD death rates among women have been reported in Canada. In 2000, for the first time, the number of women dying from COPD surpassed the number of men dying from COPD in the US. The increasing prevalence of COPD among women is felt to reflect historical trends in smoking habits. There is also evidence to suggest that women are more susceptible to the harmful effects of tobacco. In its recent COPD National Report Card, the Canadian Lung Association warns that COPD is becoming a crucial women’s health issue.

Despite these alarming trends, relatively little is known about gender differences in the manifestations, prognosis and response to treatment of patients with COPD. As noted by Becklake and Kauffman, often “in population-based studies of airway disease, gender is considered a standardizing variable rather than a determinant worthy of investigation in its own right.” Recent studies have examined differences in the clinical presentation and management of patients with COPD. Women tend to be younger and have a lesser smoking history in pack-years than men, yet report more severe dyspnea. For a similar clinical presentation, physicians are less likely to make the diagnosis of COPD in women than in men. In a primary-care setting, Dales et al. showed that women were more likely to be prescribed respiratory medications than men, independent of differences in the severity of airflow obstruction. Modification of the effect of these medications by sex has not been systematically examined. In a study of lung
function decline in asthma, treatment with inhaled corticosteroids was associated with a reduction in the decline in FEV\textsubscript{1} in men but not women\textsuperscript{13}. A recent study of sex differences in the survival of oxygen-dependent patients with COPD showed that women had a significantly higher risk of death compared with men\textsuperscript{14}.

In a large cohort of individuals with chronic airflow obstruction hospitalized for a COPD exacerbation, we questioned whether differences existed in the treatment and outcome of disease, according to gender. More specifically, we compared baseline characteristics of male and female patients including co-morbidities, respiratory medications prescribed, and markers of disease severity. We examined gender differences in mortality, and rate of re-hospitalization for COPD. We questioned whether prior hospitalization for COPD and asthma, or certain co-morbidities, differentially affected outcome in men and women.

This thesis follows the guidelines of the McGill Faculty of Graduate Studies Thesis Office. It begins with a review of the current medical literature on differences between men and women in the prevalence, diagnosis, management, and outcome of COPD. Gender differences in the susceptibility to the effects of tobacco smoke are also explored. The sources of data and analyses performed are detailed in the methods section, and results are presented. Tables and figures illustrate key findings, and are listed following the table of contents. In the discussion, the main study findings are summarized and placed in the context of current literature, and finally overall conclusions are drawn. A complete reference list and appendices are found at the end of the manuscript.
Literature Review

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of morbidity and mortality worldwide. COPD is a preventable and treatable respiratory disease characterized by progressive airflow limitation that is not fully reversible\(^1\). This chronic airflow obstruction is associated with persistent inflammation, and results from a variable combination of small airways narrowing and parenchymal destruction\(^{15}\). Systemic manifestations are also typical of COPD, and co-morbidities may contribute significantly to disease severity.

The most significant risk factor for COPD worldwide is cigarette smoking\(^1\). Air pollution and occupational exposures are other recognized risk factors. The proportion of smokers who develop COPD is commonly quoted at 15\(^{\%}\)^{16;17}, although recent evidence suggests 20-25\(^{\%}\) may be a more accurate estimate\(^{18}\). Only 5-12\(^{\%}\) of patients who develop COPD have never smoked\(^{19}\).

COPD was ranked sixth leading cause of death in 1990, but is expected to become the third leading cause of death worldwide by the year 2020\(^2\). While historically, COPD prevalence and mortality were far greater among men then women, trends have changed significantly in recent years. In the year 2000, for the first time, more women than men died of COPD in the United States\(^5\). The Canadian Lung Association recently reported that “COPD increasingly needs to be understood as a crucial women’s health issue”\(^8\).

The increasing burden of COPD in women has been attributed to historical trends of smoking rates and changing patterns of occupational exposures\(^3\). Women may also have increased susceptibility to the harmful effects of tobacco smoke\(^6\), and gender differences in airway behavior throughout the human lifespan have been described\(^9\). This review begins with a look at current trends in the prevalence of COPD in men and women. Gender differences in lung development and airway behavior are explored, and the role of tobacco and other exposures in increasing the burden of COPD in women are discussed. Current knowledge regarding gender influence on the clinical presentation and management of COPD is reviewed and future directions for research are proposed.
The terms “sex” and “gender” are frequently used interchangeably in the literature, and the distinction between the two can be confusing\textsuperscript{20,21}. Sex has generally been used to refer to strictly biological differences between women and men, related to chromosomal complement and hormones. Gender refers to a person’s self-representation as male or female; it is rooted in biology and shaped by environment and experience\textsuperscript{21,22}. An effort is made to adhere to these definitions throughout this review. The more comprehensive term “gender” is used most frequently, however, to acknowledge the complex interactions between biological, environmental and socio-cultural factors\textsuperscript{23}.

1) Trends in the prevalence of COPD

Obstructive lung diseases, including COPD and asthma, are leading causes of mortality in North America. A review of death records compiled by the US National Center for Health Statistics from 1979 through 1993 revealed that mortality rates of obstructive lung disease were starting to stabilize among men, but continued to increase in women\textsuperscript{3}. Looking specifically at COPD, between 1980 and 2000 the COPD death rate in women increased from 20.1/100,000 to 56.7/100,000, compared with a more modest increase in men, from 73/100,000 to 82.6/100,000. In the year 2000, the CDC reported 59,936 women died of COPD in the United States, compared to 59,118 men\textsuperscript{5}.

Similar trends have been observed in Canada and the UK. Using Health Statistics data from Statistics Canada, Lacasse et al reported that between 1980 and 1995, the age-standardized mortality rate from COPD doubled in Canadian women (8.3/100,000 in 1980 to 17.3/100,000 in 1995) while it remained stable in men (around 45/100,000)\textsuperscript{4}. From 1990 to 1997, the prevalence of physician-diagnosed COPD in British women rose continuously from 0.8% to 1.4%, reaching the level observed in men in 1990. In contrast, the prevalence of COPD in men reached a plateau from the mid 1990s\textsuperscript{24}. Ageing of the world’s population is expected to result in continued increases in mortality rates for COPD, particularly among women\textsuperscript{2,15}. It must be
noted that mortality rates for COPD tend to be significantly underestimated, due to general underdiagnosis of COPD and because the primary cause of death may be coded as an alternate diagnosis such as congestive heart failure or pneumonia\textsuperscript{5,15}. Based on the Global Burden of Disease Study, COPD is projected to become the third leading cause of death worldwide by the year 2020, and tobacco-attributable mortality is expected to increase from 3.0 million deaths in 1990 to 8.4 million deaths in 2020\textsuperscript{2}.

2) Lung development and airway behavior

Sex differences in lung development and airway behavior begin in utero and occur throughout the human lifespan. At birth the lungs of girls are on average smaller than those of boys, but higher size corrected flow rates and specific airway conductance (sGaw) in female neonates suggest the ratio of their large to small airways is higher. Female neonates are at lower risk of respiratory distress syndrome, presumably due to earlier surfactant production\textsuperscript{9,25}.

The sex differences in lung size apparent in infancy persist throughout childhood and adolescence, and into adulthood. Female lungs tend to be smaller than male lungs. Height is the most important determinant of the level of lung function attained. In adolescent girls, lung function increases until somatic growth ceases, whereas the lung function growth of adolescent boys continues after growth in height has stopped, into their mid20s\textsuperscript{9,25}. Adolescent boys also generate higher maximum respiratory pressures than girls; this is related to the development of muscle power under the influence of male sex steroid hormones.

While the lungs of girls and women remain smaller than those of boys and men of the same height, they exhibit higher forced expiratory flow rates (standardized for differences in body size). This phenomenon has been explained by the concept of dysanapsis. The adult female lung is the result of proportional growth of its airways in relation to its parenchyma, whereas in the adult male the growth of the airways lags behind that of the lung parenchyma (dysanaptic
growth)\textsuperscript{26}. The predicted values of the FEV1/FVC ratio standardized for differences in body size are thus higher for girls and women.

After the age of 30, changes in lung morphometry and mechanical properties begin to occur (decreased lung elastic recoil related to alterations in lung connective tissue, decreased maximum expiratory flow rates and airway closure at higher lung volumes). These age-related changes tend to develop later and occur more slowly in women than in men\textsuperscript{9}.

Sex differences in lung development and airway behavior throughout the human lifespan may contribute to the observed differences in susceptibility to noxious particles or gases, in particular tobacco smoke, and the varied manifestations of obstructive airways diseases in men and women. The evidence pointing towards an increased susceptibility of women to the harmful effects of tobacco smoke is reviewed in the next section, following an overview of the historical evolution of women’s rapport to cigarette smoking.

3) \textbf{Risk factors for COPD}

Cigarette smoking is by far the most important risk factor for COPD. The changing prevalence patterns of COPD in men and women reflect historical trends in tobacco use over the course of the twentieth century. Tobacco use by women was unusual at the turn of the twentieth century, but changing social conventions and clever marketing by the tobacco industry led to widespread adoption of cigarette smoking by women. The epidemic of tobacco use among women is expected not to reach its peak until well into the 21\textsuperscript{st} century.

There are about 200 million women who smoke worldwide. An estimated 22\% of women smoke in developed countries. In developing countries only 9\% of women smoke, but because more women live in developing countries, they constitute a larger group of smokers. The proportion of women smokers in developing countries is expected to rise to 20\% by 2025, unless appropriate measures to reduce smoking uptake by young women and increase smoking
cessation rates are implemented. This would mean that by the year 2025, the number of women smokers worldwide would exceed 500 million\textsuperscript{27}.

Smoking was not considered a publicly acceptable habit for women at the turn of the twentieth century. The prevalence of smoking in women in 1924 was estimated at 6\%, and women consumed only 5\% of all cigarettes. A woman smoking in public was therefore challenging convention, exhibiting a traditionally male behaviour. Smoking became a “symbol of emancipation”. The tobacco industry envisioned a marketing strategy based on the changing social trends, and did not miss the opportunity to double the market population consuming cigarettes\textsuperscript{28}. Ultimately, smoking was successfully linked to the ideal of a new American woman, independent and glamorous.

Tobacco marketers also recognized the evolution of women’s fashion towards slimness as a measure of beauty. American Tobacco launched the slogan “Reach for a Lucky instead of a Sweet” to promote their premier cigarette, Lucky Strikes. Phillip Morris was only slightly more subtle in 1968, when they launched a cigarette designed specifically for women named “Virginia Slims”. The still relevant theme of women’s rights was again used for the purpose of promoting cigarette sales, with slogans such as “You’ve come a long way, baby”\textsuperscript{28}.

In 1964, the landmark US Surgeon General’s report on smoking and health causally linked cigarette smoking to lung cancer in men. Other findings included increased age-specific death rates in smokers, and increased death rates from coronary artery disease in male smokers. The prevalence of smoking among women was still lagging behind that of men, but the health consequences of smoking for women soon became apparent. The 1980 Surgeon General’s report on the Health Consequences of Smoking for Women confirmed that mortality rates were increased in female smokers, similarly to male smokers, and warned of the rapidly rising lung cancer and COPD death rates in women.

There is evidence to suggest that women are more susceptible than men to the harmful effects of tobacco smoke. The results of two large European studies of smoking and lung function were reviewed by Prescott and colleagues: the Copenhagen City Heart Study (CCHS) followed 13,897 subjects, while the
Glostrup Population Study (GPS) included 4,814 subjects. Based on cross-sectional data analysis, the excess loss of FEV1 per pack-year of smoking was estimated at 7.4 ml for women and 6.3 ml for men in the CCHS. The corresponding loss in the GPS was 10.5 ml for women and 8.1 ml for men. A cross-sectional study conducted in Beijing also suggested that the adverse effect of smoking on lung function was greater among female than male smokers.

Early studies examining the impact of smoking did not support the idea of an increased susceptibility of women to the effects of tobacco. The British Physicians Study followed a large group of physicians to determine the impact of behaviours such as smoking. Between 1951 and 1973, 6,194 women and 34,440 male physicians were tracked. Both male and female smokers had increased mortality rates from emphysema and bronchitis compared with their non-smoking counterparts, and the risk of developing COPD appeared related to the amount of tobacco consumed, rather than gender. More recently, after an 11-year follow-up of the Lung Health Study participants, Anthonisen et al concluded that lung function loss is similar in men and women who continue to smoke.

The effect of cigarette smoking on lung function in adolescent boys and girls was examined in a US cohort of 5158 boys and 4902 girls, who were examined annually between 1974 and 1989. Cigarette smoking was associated with impaired lung function growth, and adolescent girls appeared to be more vulnerable than boys to this effect. In the large EPIC-Norfolk cohort, childhood smoking was found to be an independent risk factor for the development of obstructive airways disease in women. A systematic review and meta-analysis of population-based cohort studies examining longitudinal loss of lung function concluded that female current smokers had a significantly faster annual decline in FEV1 percent predicted, with increasing age, than their male counterparts.

COPD is thought to result from harmful environmental exposures in a genetically susceptible host. This complex interaction may be gender specific. A study of 84 probands with severe, early-onset COPD found a very high prevalence were women (71.4%). Among the first-degree relatives of the early-onset COPD probands, women who were current or ex-smokers were found to have
significantly lower FEV1/FVC (percent predicted) ratios and greater bronchodilator responsiveness. There is also a preponderance of women in the 5-12% of people with COPD who are non-smokers. A recent prospective study of 25 non-smokers with COPD again found a predominance of affected women. Two distinct pathologic subgroups were identified, one with significant sputum eosinophilia and the other with raised sputum neutrophil count. Organ-specific autoimmune disease was present in a third of the patients with sputum neutrophilia; this finding is intriguing as autoimmune diseases are generally more prevalent in women than men.

Although some controversy remains, there is much data to suggest a greater loss in lung function as a result of tobacco exposure in women than men. Meanwhile, tobacco companies continue to aggressively market their product to women. With increasing regulations to the marketing and sale of tobacco products in the Western world, interest has shifted to the developing world, particularly Asia. Alarming rises in smoking rates among women are predicted, unless adequate preventive measures are implemented globally.

In addition to tobacco smoke, other risk factors for COPD include air pollution, infections and occupational exposures. Air pollution disproportionately affects women in the developing world, where coal and biomass (dung, crop residues and wood) are used for cooking and heating. Emphysema develops in up to 12% of HIV-positive patients, and HIV-positive smokers are at risk for accelerated emphysema. Limited control over their sexuality is thought to place women at particular risk for HIV infection in many societies. Occupational exposures related to mining have long been linked to the development of COPD. Exposure to sensitizing agents in the predominantly female textile industries can result in airway hyperresponsiveness, and lead to fixed airflow obstruction. Finally, socio-economic factors may contribute to the rising prevalence of COPD in women. The risk of developing COPD is inversely associated with socio-economic class, and poverty disproportionately affects women worldwide, with over 70% of the estimated 1.3 billion people living in poverty being female.
4) Diagnosis of COPD

The diagnosis of COPD should be entertained in any patient who has dyspnea, chronic cough or sputum production, and a history of exposure to risk factors for the disease. Quantification of the degree of airflow obstruction using spirometry is necessary to establish the diagnosis of COPD. A post-bronchodilator FEV1/FVC ratio < 0.70 defines airflow limitation that is not fully reversible, and confirms the diagnosis1;15.

Under-recognition of COPD remains a significant problem, and many patients already have advanced disease at the time of diagnosis. This is partly attributable to the underuse of spirometry among primary care practitioners40. Insufficient clinical suspicion of symptomatic patients, particularly women, and limited awareness of the general public, compound the problem.

As described by Chapman, for many physicians in North America “the term COPD still conjures up the image of an elderly man, plagued by cough, wheeze, and breathlessness after many years of cigarette smoking so that his golden years of well deserved retirement are instead a misery of chronic illness and death by suffocation”. This stereotype is outdated and misleading6.

The existence of physician bias against diagnosing COPD in women was illustrated by a survey of 192 primary-care physicians, who were presented with a hypothetical case of cough and dyspnea in a smoker, with various versions of the case differing only in the sex and age of the patient. COPD was given as the most probable diagnosis significantly more often for men than women11.

The likelihood of a diagnosis of COPD being made increased once objective information (i.e. spirometry) was provided, yet only 22% of physicians requested spirometry after initial presentation. This again emphasized the limited use of spirometry by physicians, which is felt to be largely due to lack of comfort with interpretation. Underuse of spirometry may particularly affect women, as suggested by the Confronting COPD Survey, where women were less likely to have undergone spirometry than men (OR 0.84, 95% CI 0.72-0.98) but more likely to have received smoking cessation advice41.
5) Clinical manifestations of COPD

There is evidence to suggest that the physiologic changes typical of COPD are associated with different clinical manifestations in men and women. The Confronting COPD Survey, conducted in Europe and North America in 2000, included 3265 subjects (41% women) who were at least 45 years old and had a minimum cumulative cigarette consumption of 10 pack-years. On average women were slightly younger than men (mean age 61.2 versus 64.4 years old) and had significantly lower pack-years of smoking (mean pack-years 36.9 versus 46.6). Women were more likely than men to report severe dyspnea (OR 1.30 95%CI 1.10-1.54), with similar cough and less sputum (OR 0.84 95% CI 0.72-0.98).

Gender differences in the clinical expression of disease were explored in 53 FEV1-matched men and women with COPD attending a pulmonary clinic\textsuperscript{10}. Women tended to be younger and have a lesser smoking history in pack-years than men. Despite having the same % predicted FEV1 and a higher mean PaO2, women had a significantly shorter 6-minute walking distance and a higher degree of dyspnea. Women had a lower BMI, and a higher proportion had a BMI $\leq 21$. Finally, women were noted to have fewer co-morbidities, but more COPD exacerbations in the previous year than men.

In a rural primary-care setting, subjects 35 years and older who were current or ex-smokers, completed a respiratory questionnaire and spirometry\textsuperscript{12}. Men smoked more than women, and were more likely to have a pre-bronchodilator FEV$_1$/FVC $< 70\%$ (22.4 versus 11.8%). However, more women reported breathlessness, a prior diagnosis compatible with airflow obstruction and taking respiratory medications (23.4 versus 14.9%).

Sex differences in the manifestations of severe pulmonary emphysema were examined in the 1053 patients (38.8% female) evaluated for lung volume reduction surgery (LVRS), as part of the National Emphysema Treatment Trial\textsuperscript{42}. Female patients were slightly younger (mean age 65.4 versus 67 years, $p = 0.0001$) and had slightly lower BMI (mean BMI 24.4 versus 25 kg/m$^2$, $p=0.007$). Women reported significantly shorter smoking histories (mean pack-years 54.8
versus 71.1) and an older age at the onset of smoking (mean age 17.7 versus 16.0 years). The six-minute walk test and maximal exercise capacity were lower in women, despite slightly less severe airflow obstruction (higher post-bronchodilator FEV1 % predicted than men). Radiographic assessment revealed that the proportion of whole-lung emphysema was lower in women, with less peripheral involvement. Histological assessment in a subgroup of 101 patients (41.6% female) revealed anatomically smaller airway lumens with disproportionately thicker airway walls in women.

The relationship between lung function and COPD symptoms was examined in 816 men and 312 women completing 3 years of follow-up in EUROSCOP (European Respiratory Society Study on Chronic Obstructive Pulmonary Disease)\(^4^3\). Similar proportions of men and women reported symptoms. However, only in males was a higher baseline FEV1 % predicted associated with reduced symptoms of wheeze and dyspnea, and only in males did annual FEV1 improvement result in decreased prevalence of symptoms. In a subgroup of 178 female and 464 male Euroscop participants who were smokers unexposed to inhaled steroids, women with more severe airflow obstruction (FEV1/FVC less than median) lost 32 ml/year more of lung function than women with less severe obstruction, a difference larger than men (8 ml/year)\(^4^4\). These results suggest that not only the clinical presentation of COPD, but also the clinical course and rate of change in lung function may differ by gender.

Airway hyper-responsiveness (AHR) has been implicated as a risk factor for accelerated lung function decline, and gender differences in the prevalence of AHR in patients with COPD have been reported. Airway hyper-responsiveness refers to the sensitivity of the airways to various physical or pharmacological stimuli that induce bronchoconstriction\(^4^5\). The participants of the Lung Health Study were smokers between the ages of 35 and 60 years, who had mild COPD. Greater prevalence of AHR was noted in the women enrolled in the study. When baseline FEV1 was added to a model predicting AHR however, the effect of female gender was eliminated. The authors concluded that the higher prevalence of AHR in women was related to their smaller airway caliber\(^4^6\).
A French population-based survey of 20-44 year old subjects also reported a higher prevalence of bronchial hyper-responsiveness to methacholine among women than men. In this study, the effect of gender persisted after adjustment for airway caliber and lung size using various lung function parameters, suggesting airway size was not the culprit for the increased AHR found in women. Predictors of bronchial hyper-responsiveness to methacholine were also examined in a large Italian population study. The slope of the methacholine dose-response curve, after natural log transformation, was significantly higher in female subjects after adjusting for baseline lung function. A significantly higher slope was also noted in female current smokers, compared with ex- or never-smokers, an effect which was not observed in male subjects.

The excess prevalence of AHR in women with COPD may thus relate to smaller airway caliber, greater tobacco susceptibility, or other factors. Airway hyper-responsiveness is an independent risk factor for an accelerated decline in FEV1, and in the Lung Health Study was an important predictor of progression of airway obstruction in continuing smokers with early COPD. More recently, AHR has been linked to increased mortality in subjects with COPD.

The importance of the systemic manifestations of disease and co-morbidities associated with COPD are increasingly recognized. A co-morbidity is defined as a distinct disease entity coexisting with the primary disease of interest. Co-morbid conditions contribute to disability in the individual patient, and can complicate management. The more frequent co-morbidities associated with COPD include cardiovascular disease, osteoporosis, cachexia and malnutrition, peripheral muscle dysfunction, and malignancy.

In a multi-center study of out-patients with COPD conducted in the Netherlands, the prevalence of nutritional depletion, defined as body mass index (BMI) $\leq 21 \text{ kg/m}^2$ and/or fat-free mass index (FFMI) $\leq 15$ (females) or 16 (males), was found to be high (27%). The prevalence of low BMI and low FFMI was significantly higher in women compared to men, 18% and 40% versus 10% and 20%, respectively (both p values < 0.01).
The prevalence of anxiety and depression were also found to be high (28.2% and 18.8%, respectively) in patients with COPD compared to sex- and age-matched healthy controls (6.1% and 3.5%). Women had a higher prevalence of anxiety and depression than men (38.3% versus 25.3% and 38.3% versus 12.9%, respectively), and worse symptom-related quality of life. Women also reported a higher level of dyspnea than men for the same level of ventilatory impairment. In patients with severe emphysema evaluated for LVRS, women also reported greater breathlessness and depression, despite similar health status.

The perception of dyspnea results from the interplay of physical, emotional and cognitive factors. Anxiety and/or depression may contribute to the perceived level of breathlessness. Conversely, functional impairment due to dyspnea could worsen symptoms of anxiety or depression. Anxiety was found to be a risk factor for re-hospitalisation for COPD in a prospective study of over 400 patients with COPD. Certain co-morbidities, such as chronic renal failure and ECG signs of ischemic heart disease, have been found to predict mortality in patients with COPD. Much remains to be understood about the impact of gender on the clinical manifestations of COPD. Current knowledge regarding the influence of gender on the management and outcome of patients with COPD is also limited, and is reviewed hereafter.

6) Gender differences in management and outcome

Only two interventions to date have been shown to alter the disease course in patients with COPD. Smoking cessation is the single most effective measure to reduce the progression of airflow obstruction, and can have a substantial effect on subsequent mortality. Long-term oxygen administration in hypoxemic COPD patients has been shown to increase survival. None of the existing medications for COPD have been shown to alter lung function decline or increase survival. Pharmacotherapy is therefore used to decrease symptoms and/or complications.

The effect of smoking cessation on lung function was examined in male and female participants of the Lung Health Study. Women who became
sustained quitters had an average improvement in FEV1 % predicted during the first year that was 2.3-fold larger than was noted in men. Across a 5-year follow-up period, female sustained quitters still gained more in FEV1 % predicted than did men. Although they stand to benefit most from smoking cessation, data suggests women have more difficulty quitting than men (with nicotine replacement therapy)\textsuperscript{59}, and suffer a higher rate of relapse\textsuperscript{60}. It has been suggested that gender-specific smoking cessation programs should be developed\textsuperscript{27,28}.

Gender differences in treatment effect on symptoms and lung function decline have not been examined systematically in patients with obstructive airways diseases. Data from the Euroscop revealed that the likelihood of being treated with an inhaled corticosteroid was similar in men and women. However, ICS treatment resulted in reduced phlegm prevalence in men only\textsuperscript{43}. In a study of the effect of inhaled fluticasone on airway responsiveness in treatment-naïve individuals, the benefit of treatment was found to be significantly greater in males than females.\textsuperscript{61} The long-term effects of inhaled steroids were examined in a group of adult patients with moderate to severe asthma. Treatment with ICS was associated with a reduction in FEV1 decline in men who had smoked < 5 pack years; this effect was dose dependent, and was not present in women.\textsuperscript{13}

The survey of rural primary-care practices conducted by Dales et al\textsuperscript{12} revealed that women with mild to moderate airflow obstruction were twice as likely as males to be prescribed respiratory medications; treatment was more equal in the face of severe airflow obstruction. In the Confronting COPD Survey, women were less likely than men to have undergone spirometry (OR 0.84, 95% CI 0.72-0.98). It appears women may sometimes be prescribed respiratory medications inappropriately, without a relationship to airflow obstruction or a clear diagnosis, increasing the possibility of adverse events without definite efficacy. Women are likely to be at higher risk than men for certain side effects, such as osteoporosis with inhaled or oral corticosteroids.

In patients with COPD requiring long-term oxygen therapy (LTOT), sex differences in survival have been reported. A seven-year prospective study of 435 out-patients with COPD requiring LTOT was conducted in Sao Paulo, Brazil.\textsuperscript{14}
After adjusting for potential confounders (age, pack-years smoked, PaO2, FEV1, body mass index), women were found to be at significantly higher risk of death (HR 1.54, 95% CI 1.15-2.07). A prior Japanese study\textsuperscript{62} examined the effect of gender on prognosis in a large population of patients receiving LTOT, and found women had a better prognosis than men. However, the range of patient diagnoses included COPD, sequelae of tuberculosis and chronic interstitial pneumonia, and this may explain the difference in findings.

Sex differences in mortality were also examined in a large population-based cohort of Barcelona patients who visited the ER for COPD or asthma\textsuperscript{63}. A total of 15,517 individuals, 9,918 men and 5,599 women were included in the study. The mortality rates for both males and females were significantly higher than the expected rates in the general population. The relative increases in mortality rates for both asthma and COPD, when comparing with the general population, were significantly higher in women than men. However, within the study cohort, survival was better in females than males.

7) Future directions

The evidence reviewed does suggest that gender differences exist in the clinical expression, evolution, treatment and outcome of COPD. Many questions remain to be answered, and areas for future investigation were delineated in a recent commentary by Han and colleagues\textsuperscript{21}. There is a need to clarify to what extent tobacco susceptibility differs between men and women, as well as develop and evaluate gender-specific approaches to quitting. Further research into gender differences in the manifestations and clinical course of COPD is warranted. In addition, therapeutic trials should have sufficient power to allow a separate assessment of treatment response in men and women. As hoped for by Becklake and Kauffman\textsuperscript{9}, gender must be considered “a variable worthy of investigation in its own right”, and not a simple “standardizing variable”.

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OBJECTIVES

In a large 1990s cohort of patients dispensed medications used in the treatment of chronic airflow obstruction and hospitalized for COPD, we sought to determine whether gender differences existed in the treatment and outcome of disease. We compared baseline characteristics of male and female patients including respiratory medications dispensed in the year prior to cohort entry, markers of disease severity, and co-morbidities. We examined gender differences in mortality and rate of re-hospitalization for COPD, following discharge from the index COPD hospitalization.

1. To describe gender differences in patient characteristics including respiratory medications dispensed, severity of respiratory disease and existing co-morbidities, in the year prior to the index COPD hospitalization

2. To examine gender differences in the respiratory medications dispensed in the year following the index COPD hospitalization

3. To compare mortality (including causes of death) and rate of rehospitalization for COPD and asthma in male and female patients, following discharge from the index COPD hospitalization
METHODS

Source of data

The databases from the Québec provincial health insurance plan were used. The Régie de l’Assurance Maladie du Québec (RAMQ) administers the universal health insurance program for the seven million residents of the province of Québec, Canada. The databases contain information on demographics (age, sex, region of residence), medical services rendered, diagnoses, and outpatient prescriptions. The three main databases are the physician services claims, the outpatient prescription claims, and the data on hospitalizations (med-echo). Each patient is identified by a unique number, which is encrypted to protect confidentiality. All medical services rendered, whether during hospitalization or in an outpatient setting, are accompanied by ICD-9 or ICD-10 diagnostic codes and compiled in the physician claims database. This includes all diagnostic and therapeutic procedures. The cost of all outpatient prescriptions is covered for individuals aged 65 years and older, and details of the medications prescribed (drug name, form, dosage, dispensation date) are contained in the prescription claims database. However, this information is not available for medications prescribed during hospitalizations. The accuracy and comprehensiveness of the prescription claims database of Québec has been verified previously. The med-echo (hospitalization) database comprises the information contained in standardized hospital discharge summaries, and specifies the principal diagnosis that led to hospitalization. Vital statistics are obtained from l’Institut de la Statistique du Québec (ISQ).

Study design

Subjects with chronic airflow obstruction were identified using dispensed prescriptions for the following respiratory medications: any form of β-agonist, theophylline, ipratropium bromide or inhaled corticosteroids (ICS). Patients who received three or more prescriptions for these respiratory medications in any one-year period, dispensed on at least two separate occasions, were selected. The third
prescription for a respiratory medication had to occur between January 1st 1990 and December 31st 2001, in a patient aged 66 years or older, and be preceded by at least one year of prescription information in the database. Requiring the third prescription to occur after the age of 66 years ensured that most patients had at least one year of prior prescription information available. The date of either the third prescription, or the earliest subsequent prescription meeting the above criteria, was taken as the date of entry into the study population.

No specific attempt was made to exclude asthmatics, other than by selecting respiratory medications which can be used in the treatment of either COPD or asthma, and excluding medications which guidelines recommend for the treatment of asthma only (sodium cromoglycate, nedocromil, ketotifen and leukotriene antagonists).

The study cohort consisted of all subjects with a first hospitalization for a primary diagnosis of COPD after selection into the study population. Cohort entry (t0) was taken as the date of discharge from this first hospitalization for COPD (ICD-9 codes 490, 491, 492, 496 and ICD-10 codes J40, J41, J42, J43 and J44). Details of the ICD-9 and ICD-10 codes used to define COPD hospitalizations are shown in Appendix 1. All patients in the study cohort were followed until death or December 31st, 2003. The date of death was taken as the earliest date recorded in either the ISQ or RAMQ databases.

Cohort description

Age at the time of the index hospitalization (t0) and length of database follow-up preceding and following cohort entry were calculated for each individual. Mean values for men and women in the cohort were calculated.

All hospitalizations for COPD, occurring either before or after t0, were identified for each subject in the med-echo database, using the ICD-9 and ICD-10 codes listed above. Hospitalizations with a primary diagnosis of asthma were identified using the ICD-9 code 493 (asthma) and ICD-10 codes J45 (asthma) and J46 (status asthmaticus). Prior obstructive airways disease (OAD) hospitalizations, defined as a hospitalization with a diagnosis of either COPD or
asthma, were also tabulated. Finally, hospitalizations for cardiovascular diseases occurring prior to t0 were documented, using the appropriate ICD-9 (410-414, 145-417, 425-427, 428, 430-438) and ICD-10 codes (I20-I25, I26-I28, I42-I49, I50, I60-I69).

All outpatient prescriptions dispensed in the year prior to, and following the index date, were obtained from the prescription claims database. Prescriptions were extracted after compiling of detailed list of the various identifier codes for medications of interest (code DIN, code de denomination commune) between 1990 and 2003. For each subject, the number of prescriptions for the following respiratory medication classes was tabulated: bronchodilators (β-agonists and ipratropium bromide), theophylline, inhaled corticosteroids, oral corticosteroids and antibiotics used in the treatment of respiratory tract infections (designated as “respiratory antibiotics” in the text). The mean number of prescriptions of each class dispensed to both men and women, and the proportion of men and women in the study cohort dispensed these medications, were examined in the 1-year periods preceding and following the index hospitalization. The effect of the index hospitalization on modifying prescription patterns of various respiratory medications in men and women was also examined.

Co-morbidities were measured using prescriptions for various classes of medications associated with the treatment of the disorders of interest, dispensed in the year prior to cohort entry (see Appendix 2). Diabetes was defined by dispensed insulin or an oral hypoglycemic agent; cardiovascular disease by a prescription for cardiotropes, anti-hypertensives, diuretics, vasodilators or anti-platelet agents; central nervous system drugs (CNS) included major tranquillizers, anticonvulsants and drugs for parkinsonism of Alzheimer’s dementia; osteoporosis drugs included calcium, vitamin D and biphosphonates; rheumatic drugs included gold salts, methotrexate, azathioprine, chloroquine, hydroxychloroquine and sulfasalazine. Use of the newer anti-tumor necrosis factor α agents was minimal in this cohort. Prescriptions for benzodiazepines, anti-depressant medications, non-steroidal anti-inflammatory drugs (NSAIDS), and narcotics were also compiled and considered as separate categories.
The severity of respiratory disease was quantified using the number of prescriptions of respiratory medications (β-agonists, ipratropium bromide, theophylline and inhaled corticosteroids), oral corticosteroids, and respiratory antibiotics, all dispensed in the year prior to the index hospitalization. The occurrence of hospitalization with a primary diagnosis of COPD or asthma in the year prior to t0 was also considered.

To ensure accuracy and completeness of the list of identifier codes used to examine respiratory medications of interest, trends in the medications dispensed were examined over the interval of 1990 to 2003. The patterns observed were compared with previously reported trends and/or patterns of medication use expected based on the evolution of clinical practice during this period.

Survival and cause of death

Date of death was obtained from the ISQ (Institut de la Statistique du Québec). Cause of death, as reported by the physician who completes the death certificate, is also documented within the ISQ database (“cause médicale du décès”). This was tabulated using the appropriate ICD-9 and ICD-10 codes.

Statistical analysis

For the descriptive analyses of men and women in the cohort, no statistical analyses were performed (Student’s t-test, Chi-square) since no hypotheses were being tested. The Kaplan-Meier method was used to estimate time to death and time to first re-hospitalization for COPD and Obstructive Airways Disease (OAD = COPD or asthma). Cox’s proportional-hazards models were used to determine the effect of male gender on death and repeat hospitalization for COPD, OAD, and all causes. The proportionality of hazards was verified using a graphical method. The analyses were adjusted for age, asthma or COPD hospitalization in the year prior to t0, co-morbidities and respiratory medications dispensed in the year before cohort entry. A p-value of 0.05 was considered statistically significant. All analyses were conducted using SAS version 9.1. Certain graphs were designed using GraphPad Prism.
RESULTS

Study cohort

The study population comprised 195,049 individuals receiving treatment for chronic airflow obstruction. These individuals were over 66 years of age, and had received three or more prescriptions for the specified respiratory medications, within a one-year period and on at least two separate occasions, between January 1st 1990 and December 31st 2001. From this group, 45,708 patients were hospitalized with a primary diagnosis of COPD. A total of 2,555 patients were excluded: 2,506 patients who died during the index hospitalization or on the day of discharge, and 49 individuals for whom the date of end of follow-up was found to be inconsistent across the various databases.

The study cohort thus consisted of 19,260 women and 23,893 men (total 43,153 individuals) who were discharged from a first COPD hospitalization following selection into the study population. Details of the baseline characteristics of women and men in the study cohort are displayed in Table 1. The mean age of women was 77.5 years (SD 6.5 years) and men 77.3 years (SD 6.2 years). The mean duration of follow-up in the study cohort after the index hospitalization was 3.7 years (SD 3.0 years). All subjects had a minimum of one year of follow-up in the database prior to cohort entry, and the mean duration of available data before t0 was 7.6 years (SD 3.5 years).

Based on the definitions of the study population and cohort, hospitalizations prior to cohort entry were possible i.e. before selection into the study population. However, the majority of patients in the study cohort (86.9% of individuals) had no prior COPD hospitalizations. Specifically, only 2.7% of women and 2.6% of men were hospitalized for COPD in the year prior to the index hospitalization, and 13.5% of women and 12.8% of men were ever hospitalized for COPD prior to the index hospitalization (t0). When hospitalization with a primary diagnosis of asthma were examined, 3.4% of women and 1.6% of men had been hospitalized in the year prior to t0. Women were more likely than men to have been previously hospitalized for asthma, with
9.8% of women in the cohort versus 4.2% of men having had an asthma hospitalization anytime before t0. One or more hospitalizations for obstructive airways diseases (either COPD or asthma) occurred in 6.0% of women and 4.1% of men, in the year prior to cohort entry.

Co-morbidities

The proportion of subjects with various co-morbidities, based on medications dispensed in the year prior to cohort entry, is shown in Table 2 (2a). The mean number of comorbidity-defining prescriptions dispensed to men and women, in the year prior to t0, is shown in Table 2b. The prevalence of diabetes, CNS disease, and rheumatic disease were similar in men and women. A slightly larger proportion of women were prescribed cardiovascular medications in the year before cohort entry (78.5% versus 71.9%), and a larger proportion received osteoporosis medications (13.6% versus 3.8%). A significantly higher proportion of women than men were dispensed benzodiazepines and anti-depressant drugs in the year prior to t0 (62.5% versus 48.7% and 20.3% versus 11.3%, respectively). The mean number of benzodiazepine and anti-depressant prescriptions dispensed to women in the year prior to t0 was also higher than for men. Finally, more women than men were dispensed narcotics and NSAIDS.

Respiratory medications

The respiratory medications dispensed are presented as mean number of prescriptions dispensed, and the proportion of subjects dispensed ≥1 prescription of each class, in the year prior to (Table 3) and after t0 (Table 4). In the year prior to t0, similar proportions of men and women received ICS and β2-agonists. However, a much smaller proportion of women were dispensed ipratropium bromide (42.5% versus 52.9% of male subjects) and theophylline (30.4% versus 40.4% of male subjects). The mean number of prescriptions for bronchodilators dispensed to women in the year prior to t0 was also smaller: for β2-agonists 6.3 versus 8.2 for men, and for ipratropium 3.3 versus 4.7 for men.
In the year following the index hospitalization, the differences in respiratory medications prescribed to male and female patients were somewhat reduced. Similar proportions of both men and women received ICS and β2-agonists, although the mean number of prescriptions for β2-agonists dispensed was still less in women than men. A larger proportion of both men and women were dispensed ipratropium bromide in the year following the index hospitalization compared to the year preceding t0, with a reduced gender gap (64.5% of women versus 71% of men dispensed ipratropium after t0).

The effect of the index hospitalization on the prescription of respiratory medications in men and women was examined, and results by medication class are shown in tables 5a to 5d. The majority of subjects receiving ICS, β2-agonists and ipratropium bromide prior to t0 were also dispensed one or more prescriptions for these medications in the year following t0. Approximately half of the subjects who were not dispensed such prescriptions prior to t0 received the medications in the ensuing one-year period. No differences between men and women were noted.

Prescriptions for oral corticosteroids and respiratory antibiotics were examined as potential markers of respiratory disease severity. The mean number of oral corticosteroid and respiratory antibiotic prescriptions dispensed to men and women in the year prior to t0 were similar; the proportion of male and female subjects dispensed such prescriptions were also comparable. In the year following the index hospitalization, an increase in the mean number of oral corticosteroids prescriptions dispensed was noted for both men and women.

Respiratory medications dispensed to men and women were examined for every one-year interval from 1990 to 2003 (mean number of prescriptions and proportion of subjects dispensed ≥ 1 prescription). All graphs are displayed in Appendix 3. There was a trend towards decreasing prescriptions for β2-agonists, and increasing prescriptions for ipratropium dispensed, in both male and female subjects. Overall prescriptions for bronchodilators (β2-agonists and ipratropium bromide combined) were stable during the study period, as where prescriptions for inhaled corticosteroids. There was a clear decline in dispensed prescriptions for theophylline between 1990 and 2003.
Mortality and time to re-hospitalization

There were 27,999 deaths over the duration of follow-up. A total of 11,245 women (58.4%) and 16,754 (70.1%) men died following cohort entry. During the first year after cohort entry, there were 2,419 women (12.6%) and 4,371 men (18.3%) who died. The mean age of women and men who died in the year following cohort entry was 80.4 ± 6.4 years and 79.8 ± 6.0 years, respectively.

Information regarding cause of death was missing from the ISQ database in 2.2% of deceased subjects. The most common cause of death in both men and women was COPD, accounting for 32% of all deaths in women and 36% of all deaths in men. A very small proportion of deaths were attributed to asthma (79/11,245 deaths in women and 38/16,754 deaths in men), so that the mortality attributed to combined OAD was similar to the reported COPD mortality. The second most common cause of death was cardiovascular diseases, responsible for 26% of all female deaths and 24% of all male deaths. Lung cancer was the documented cause of death in 7% of women and 10% of men.

Cox’s regression model was used to examine the effect of gender and other covariates on mortality and risk of re-hospitalization for OAD (Tables 9 and 10). The proportionality of death and re-hospitalization hazards was confirmed using graphical methods. Mortality risk increased with age (HR 1.82 per decade of age). After adjusting for age, COPD or asthma hospitalization in the year prior to t0, co-morbidities and respiratory medications dispensed, male gender was found to be associated with a significantly increased risk of death (HR 1.45, 95% CI 1.42-1.49). Male sex was associated with a lesser, though still significantly increased, risk of re-hospitalization for OAD (HR 1.12, 95% CI 1.09-1.15). Asthma hospitalization in the year prior to t0 was associated with significantly decreased mortality (HR 0.76, 95% CI 0.70-0.82), but a higher risk of repeat OAD hospitalization (HR 1.52, 95% CI 1.41-1.64). COPD hospitalization in the year prior to t0 did not affect survival, but increased the risk of repeat OAD hospitalization (HR 1.34, 95% CI 1.25-1.44). Diabetes and cardiovascular disease were associated with increased mortality risk and all-cause re-hospitalization, but a decreased risk of OAD re-hospitalization (HR 0.84 and 0.95, respectively).
Table 1
Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>WOMEN</th>
<th>MEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of individuals</td>
<td>19,260</td>
<td>23,893</td>
</tr>
<tr>
<td>Age in years (mean ± SD)</td>
<td>77.5 ± 6.5</td>
<td>77.3 ± 6.2</td>
</tr>
<tr>
<td>Duration of available data</td>
<td>7.8 ± 3.6</td>
<td>7.4 ± 3.5</td>
</tr>
<tr>
<td>before cohort entry in years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mean ± SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up in years (mean ±</td>
<td>4.0 ± 3.1</td>
<td>3.5 ± 2.8</td>
</tr>
<tr>
<td>SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD hospitalization anytime</td>
<td>13.5</td>
<td>12.8</td>
</tr>
<tr>
<td>before t0 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD hospitalization in the</td>
<td>2.7</td>
<td>2.6</td>
</tr>
<tr>
<td>year prior to t0 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma hospitalization</td>
<td>9.8</td>
<td>4.2</td>
</tr>
<tr>
<td>anytime before t0 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma hospitalization in the</td>
<td>3.4</td>
<td>1.6</td>
</tr>
<tr>
<td>year prior to t0 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OAD hospitalization anytime</td>
<td>21.7</td>
<td>16.1</td>
</tr>
<tr>
<td>before t0 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OAD hospitalization in the</td>
<td>6.0</td>
<td>4.1</td>
</tr>
<tr>
<td>year prior to t0 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVS hospitalization anytime</td>
<td>27.5</td>
<td>30.6</td>
</tr>
<tr>
<td>before t0 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVS hospitalization in the</td>
<td>9.4</td>
<td>10.3</td>
</tr>
<tr>
<td>year prior to t0 (%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OAD Obstructive Airways Disease (COPD or asthma)
CVS Cardiovascular Diseases
Table 2
Co-morbidities

2a) The proportion of subjects with the co-morbidity, as defined by medication classes dispensed in the year prior to cohort entry, is reported.

<table>
<thead>
<tr>
<th>Condition</th>
<th>WOMEN</th>
<th>MEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>12.7%</td>
<td>11%</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>78.5%</td>
<td>71.9%</td>
</tr>
<tr>
<td>CNS disease</td>
<td>9.9%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>13.6%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Rheumatic drugs</td>
<td>1.6%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>62.5%</td>
<td>48.7%</td>
</tr>
<tr>
<td>Anti-depressive drugs</td>
<td>20.3%</td>
<td>11.3%</td>
</tr>
<tr>
<td>Narcotics</td>
<td>3.6%</td>
<td>2.5%</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>32.7%</td>
<td>25.7%</td>
</tr>
</tbody>
</table>
Table 2 (cont’d)
Co-morbidities

2b) Mean number of comorbidity-defining prescriptions in the year prior to t0

<table>
<thead>
<tr>
<th></th>
<th>WOMEN</th>
<th>MEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>2.2 ± 8.4</td>
<td>1.7 ± 6.2</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>22.7 ± 30.4</td>
<td>19 ± 27.2</td>
</tr>
<tr>
<td>CNS disease</td>
<td>1.2 ± 6.5</td>
<td>1.1 ± 5.4</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>1.5 ± 7.2</td>
<td>0.4 ± 4.0</td>
</tr>
<tr>
<td>Rheumatic drugs</td>
<td>0.2 ± 2.0</td>
<td>0.1 ± 1.4</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>7.7 ± 11.1</td>
<td>5.3 ± 9.1</td>
</tr>
<tr>
<td>Anti-depressive drugs</td>
<td>2.2 ± 7.1</td>
<td>1.0 ± 4.6</td>
</tr>
<tr>
<td>Narcotics</td>
<td>0.2 ± 2.3</td>
<td>0.1 ± 1.6</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>1.5 ± 3.8</td>
<td>1.1 ± 3.2</td>
</tr>
</tbody>
</table>
Table 3
Respiratory medications dispensed in the year prior to t0

3a) Mean number of prescriptions dispensed in the year before t0

<table>
<thead>
<tr>
<th></th>
<th>WOMEN</th>
<th>MEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS</td>
<td>3.4 ± 4.2</td>
<td>4.1 ± 4.6</td>
</tr>
<tr>
<td>B2-agonists</td>
<td>6.3 ± 7.2</td>
<td>8.2 ± 8.7</td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>3.3 ± 5.8</td>
<td>4.7 ± 6.8</td>
</tr>
<tr>
<td>Theophylline</td>
<td>2.4 ± 5.7</td>
<td>3.5 ± 6.1</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>1.3 ± 3.7</td>
<td>1.4 ± 3.4</td>
</tr>
<tr>
<td>Respiratory antibiotics</td>
<td>1.7 ± 2.1</td>
<td>1.8 ± 2.3</td>
</tr>
</tbody>
</table>

The mean number of prescriptions dispensed (± SD) is shown.

3b) Proportion of subjects dispensed ≥ 1 prescription of each class in the year before t0

<table>
<thead>
<tr>
<th></th>
<th>WOMEN</th>
<th>MEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS</td>
<td>64.2%</td>
<td>66.7%</td>
</tr>
<tr>
<td>B2-agonists</td>
<td>79.3%</td>
<td>82.3%</td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>42.5%</td>
<td>52.9%</td>
</tr>
<tr>
<td>Theophylline</td>
<td>30.4%</td>
<td>40.4%</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>35.7%</td>
<td>37.4%</td>
</tr>
<tr>
<td>Respiratory antibiotics</td>
<td>68%</td>
<td>67.2%</td>
</tr>
</tbody>
</table>
### Table 4
Respiratory medications dispensed in the year following t0

#### 4a) Mean number of prescriptions dispensed in the year after t0

<table>
<thead>
<tr>
<th></th>
<th>WOMEN</th>
<th>MEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS</td>
<td>4.5 ± 4.5</td>
<td>4.8 ± 4.7</td>
</tr>
<tr>
<td>B2-agonists</td>
<td>6.9 ± 7.6</td>
<td>8.5 ± 9.0</td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>5.4 ± 6.9</td>
<td>6.6 ± 7.6</td>
</tr>
<tr>
<td>Theophylline</td>
<td>2.4 ± 6.2</td>
<td>3.5 ± 6.5</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>1.8 ± 4.2</td>
<td>2.0 ± 4.2</td>
</tr>
<tr>
<td>Respiratory antibiotics</td>
<td>1.7 ± 2.2</td>
<td>1.9 ± 2.6</td>
</tr>
</tbody>
</table>

The mean number of prescriptions dispensed (± SD) is shown.

#### 4b) Proportion of subjects dispensed ≥ 1 prescription of each class in the year after t0

<table>
<thead>
<tr>
<th></th>
<th>WOMEN</th>
<th>MEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS</td>
<td>74.4%</td>
<td>75%</td>
</tr>
<tr>
<td>B2-agonists</td>
<td>78.6%</td>
<td>81.4%</td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>64.5%</td>
<td>71%</td>
</tr>
<tr>
<td>Theophylline</td>
<td>28.4%</td>
<td>39%</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>44.4%</td>
<td>49%</td>
</tr>
<tr>
<td>Respiratory antibiotics</td>
<td>64.2%</td>
<td>65.5%</td>
</tr>
</tbody>
</table>
Table 5
Patterns of prescriptions of respiratory medications before, and after, the index hospitalization

5a) Inhaled corticosteroids

<table>
<thead>
<tr>
<th>ICS prescription in the year prior to t0</th>
<th>Subjects dispensed ICS in the year following t0</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOMEN</td>
<td>MEN</td>
</tr>
<tr>
<td>No</td>
<td>52.4%</td>
</tr>
<tr>
<td></td>
<td>50.8%</td>
</tr>
<tr>
<td>Yes</td>
<td>86.7%</td>
</tr>
<tr>
<td></td>
<td>87%</td>
</tr>
</tbody>
</table>

5b) β2-Agonists

<table>
<thead>
<tr>
<th>β2-agonist prescription in the year prior to t0</th>
<th>Subjects dispensed β2-agonists in the year following t0</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOMEN</td>
<td>MEN</td>
</tr>
<tr>
<td>No</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td>49.3%</td>
</tr>
<tr>
<td>Yes</td>
<td>85.9%</td>
</tr>
<tr>
<td></td>
<td>88.4%</td>
</tr>
</tbody>
</table>
Table 5 (cont’d)
Patterns of prescriptions of respiratory medications before, and after, the index hospitalization

5c) Ipratropium bromide (IPB)

<table>
<thead>
<tr>
<th>IPB prescription in the year prior to t0</th>
<th>Subjects dispensed IPB in the year following t0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WOMEN</td>
</tr>
<tr>
<td>No</td>
<td>47.9%</td>
</tr>
<tr>
<td>Yes</td>
<td>86.9%</td>
</tr>
</tbody>
</table>

5d) Theophylline

<table>
<thead>
<tr>
<th>Theophylline prescription in the year prior to t0</th>
<th>Subjects dispensed theophylline in the year following t0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WOMEN</td>
</tr>
<tr>
<td>No</td>
<td>10.5%</td>
</tr>
<tr>
<td>Yes</td>
<td>69.4%</td>
</tr>
</tbody>
</table>
Table 6
Number of deaths after cohort entry

<table>
<thead>
<tr>
<th></th>
<th>WOMEN</th>
<th>MEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of deaths following cohort entry (%)</td>
<td>11,245 (58.4%)</td>
<td>16,754 (70.1%)</td>
</tr>
<tr>
<td>Survival after t0, in years (mean ± SD)</td>
<td>4.0 ± 3.1</td>
<td>3.5 ± 2.8</td>
</tr>
<tr>
<td>Number of deaths within one year of cohort entry (%)</td>
<td>2,419 (12.6%)</td>
<td>4,371 (18.3%)</td>
</tr>
<tr>
<td>Age of subjects who die within one year of t0 (mean ± SD)</td>
<td>80.4 ± 6.4</td>
<td>79.8 ± 6.0</td>
</tr>
<tr>
<td>Number of deaths within 90 days of cohort entry (%)</td>
<td>838 (4.4%)</td>
<td>1,728 (7.2%)</td>
</tr>
</tbody>
</table>

Table 7
Cause of death

<table>
<thead>
<tr>
<th></th>
<th>WOMEN</th>
<th>MEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>3,636 (32%)</td>
<td>6,104 (36%)</td>
</tr>
<tr>
<td>CVS</td>
<td>2,917 (26%)</td>
<td>4,038 (24%)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>787 (7%)</td>
<td>1,599 (10%)</td>
</tr>
<tr>
<td>Other causes</td>
<td>3,905 (35%)</td>
<td>5,013 (30%)</td>
</tr>
<tr>
<td>Total number of deaths</td>
<td>11,245</td>
<td>16,754</td>
</tr>
</tbody>
</table>

CVS Cardiovascular disease
Table 8
Deaths and re-hospitalizations for COPD and asthma, after the index hospitalization

<table>
<thead>
<tr>
<th></th>
<th>Deaths (%)</th>
<th>Re-hospitalizations for COPD (%)</th>
<th>Hospitalizations for asthma (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>2,419 (12.6%)</td>
<td>4,371 (18.3%)</td>
<td>1,990 (10.3%)</td>
</tr>
<tr>
<td>Year 3</td>
<td>5,861 (30.4%)</td>
<td>9,754 (40.8%)</td>
<td>5,340 (27.7%)</td>
</tr>
<tr>
<td>Year 5</td>
<td>8,436 (43.8%)</td>
<td>13,430 (56.2%)</td>
<td>7,433 (38.6%)</td>
</tr>
</tbody>
</table>

The number of deaths and the total number of subjects with ≥1 re-hospitalization for COPD and asthma at one year, three years and five years after cohort entry is shown.
Table 9
Hazard ratios of mortality and re-hospitalization for COPD, OAD, and all causes, for male relative to female gender

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio (male relative to female)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.40</td>
</tr>
<tr>
<td>COPD re-hospitalization</td>
<td>1.27</td>
</tr>
<tr>
<td>OAD re-hospitalization</td>
<td>1.20</td>
</tr>
<tr>
<td>All-cause re-hospitalization</td>
<td>1.12</td>
</tr>
</tbody>
</table>

OAD Obstructive Airways Disease (COPD and asthma)

* The analysis is adjusted for age, hospitalizations for COPD or asthma in the year prior to t0, and the factors in Tables 2a and 3a.
Table 10
Contribution of other covariates to mortality and risk of hospitalization (OAD and all-cause)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Death</th>
<th>OAD re-hospitalization</th>
<th>All-cause re-hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted Hazard Ratio (95% CI)</td>
<td>Adjusted Hazard Ratio (95% CI)</td>
<td>Adjusted Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>Age (per decade)</td>
<td>1.82 (1.78-1.85)</td>
<td>0.97 (0.95-0.99)</td>
<td>1.14 (1.12-1.16)</td>
</tr>
<tr>
<td>COPD hospitalization in year prior to t0</td>
<td>0.96 (0.90-1.03)</td>
<td>1.34 (1.25-1.44)</td>
<td>1.18 (1.11-1.25)</td>
</tr>
<tr>
<td>Asthma hospitalization in year prior to t0</td>
<td>0.76 (0.70-0.82)</td>
<td>1.52 (1.41-1.64)</td>
<td>1.25 (1.18-1.34)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.13 (1.09-1.17)</td>
<td>0.84 (0.80-0.88)</td>
<td>1.11 (1.08-1.15)</td>
</tr>
<tr>
<td>CVS</td>
<td>1.18 (1.15-1.22)</td>
<td>0.95 (0.92-0.98)</td>
<td>1.15 (1.13-1.18)</td>
</tr>
</tbody>
</table>

OAD Obstructive Airways Disease (COPD and asthma)
CVS Cardiovascular disease

The analysis is adjusted for sex, and the factors in Tables 2a (co-morbidities) and 3a (respiratory medications dispensed in the year prior to t0).
Figure 1

The proportion of subjects alive (graphs 1a to 1c) or not yet re-hospitalized for OAD (graphs 1d to 1f) is shown for the first 5 years after $t_0$

a) Survival after the index hospitalization, by gender

b) Survival by gender, taking into account COPD hospitalization in the year before $t_0$
c) Survival by gender, taking into account asthma hospitalization in the year before t0

![Survival graph for gender and asthma hospitalization](image)

- Women, not hospitalized for asthma in year before t0
- Men, not hospitalized for asthma in year before t0
- Women, hospitalized for asthma in year before t0
- Men, hospitalized for asthma in year before t0

d) Time to OAD re-hospitalization, by gender

![Time to re-hospitalization graph for gender](image)

- Women
- Men

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e) Time to OAD re-hospitalization, considering COPD hospitalization in the year before t0

![Graph showing survival rates for re-hospitalization based on COPD status.]

- Women, not hospitalized for COPD in year before t0
- Men, not hospitalized for COPD in year before t0
- Women, hospitalized for COPD in year before t0
- Men, hospitalized for COPD in year before t0

f) Time to OAD re-hospitalization, considering asthma hospitalization in the year before t0

![Graph showing survival rates for re-hospitalization based on asthma status.]

- Women, not hospitalized for asthma in year before t0
- Men, not hospitalized for asthma in year before t0
- Women, hospitalized for asthma in year before t0
- Men, hospitalized for asthma in year before t0
Discussion

Although COPD was considered a typically male disease in the past, increases in female smoking over the course of the 20th century have translated into a prevalence of COPD that is still rising. Investigators only recently began focusing their attention on possible differences in the clinical expression and evolution of disease in men and women with COPD. In a large cohort of elderly patients hospitalized for COPD, we report gender differences in patient characteristics, treatment dispensed and outcome.

The study population consisted of subjects who were dispensed respiratory medications used in the treatment of obstructive airways disease. Patients then entered the study cohort upon discharge from the first COPD hospitalization which followed the initiation of outpatient respiratory medications. This was not an incidence cohort, as subjects could be hospitalized for COPD prior to their selection into the study population. A small proportion of men and women (approximately 13%) were hospitalized for COPD before meeting the requirement of having been dispensed three or more respiratory medications on at least 2 different dates, within a one-year period.

The mean age of men and women in the cohort was similar, as was the mean age of men and women who died in the first year following the index hospitalization. In previous studies of gender differences in the clinical manifestations of COPD, female subjects were reported to be younger than their male counterparts, in conjunction with a lesser smoking history. The similarity in age in our cohort is partly artificial, due to the requirement that subjects be 66 years and older to enter the study population. This was done to ensure that at least 1 year of prescription information would be available prior to cohort entry. In contrast, in the med-echo database, all hospitalizations are recorded regardless of age.

More women than men were hospitalized with a primary diagnosis of asthma prior to cohort entry. The incidence and prevalence of asthma in older women have been reported to be higher than in men. In the Tucson epidemiologic
study of obstructive lung diseases, the incidence of asthma was 1.5 times greater in young boys than girls, but greater in women older than 40 years of age\textsuperscript{65}. In the Saskatchewan Medical Claims database, the prevalence of physician-diagnosed asthma was found to be higher in boys than girls up to 14 years of age, but reversed in older age groups, with a higher prevalence in women 35 to 64 years old\textsuperscript{66}. Enright and coworkers described a group of patients with asthma in the Cardiovascular Health Study\textsuperscript{67}. Subjects were 65 years and older, non-smokers and with no congestive heart failure, and were classified as having possible, probable or definite asthma: 78% of subjects with definite asthma, and 74% of subjects with probable or possible asthma were female.

We cannot exclude that symptoms of COPD in women, despite a significant smoking history, are more likely to be labeled as “asthma” by physicians. Such physician diagnostic bias was first suspected by Burrows in the Tucson study: similar symptoms in subjects over the age of 40 years were much more likely to lead to a diagnosis of “asthma” in women than men\textsuperscript{65}. Chapman and colleagues\textsuperscript{11} reported similar findings following their survey of 192 primary-care physicians. When physicians were presented with the hypothetical case of a smoker with cough and dyspnea, COPD was given as the most probable diagnosis significantly more often for men than women, with more women receiving the alternative diagnosis of asthma.

This study suffers from the limitations typical of database analyses. Information on risk factors for COPD, particularly smoking and family history, as well as lung function records are not part of the RAMQ databases. Such limitations make it difficult to tease out a component of gender bias in diagnostic labeling from a true difference in asthma prevalence between men and women, in this cohort of patients hospitalized with a primary diagnosis of COPD. We did not consider diagnoses documented as part of medical service claims. The validity of these diagnoses has been questioned. A study conducted at a single hospital specialized in pulmonary diseases concluded that diagnostic codes from physician service claims accurately identified COPD patients\textsuperscript{68}, but Lacasse and colleagues concluded that diagnoses of COPD recorded for billing purposes lacked validity\textsuperscript{69}. 

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Co-morbidities have been defined as diseases co-existing with the primary disease of interest, regardless of whether the conditions are directly related to COPD or not. The importance of adequate recognition and management of co-morbidities in patients with COPD is increasingly being recognized\textsuperscript{15}. Co-morbidities were assessed using prescriptions for medications used in the treatment of the various disorders of interest, dispensed in the year before cohort entry. This method has been used to identify co-morbidities in several studies published by our group\textsuperscript{70,71}, and the conditions examined using dispensed prescriptions are part of the chronic disease score created by Von Korff\textsuperscript{72} for pharmaceutical database research.

Patients with COPD are at increased risk of hospitalization and death from cardiovascular diseases (CVS)\textsuperscript{73}. In our cohort, slightly more women than men were dispensed cardiovascular drugs in the year preceding the index hospitalization, with a majority of cohort subjects having received at least one cardiovascular medication before the COPD hospitalization defining cohort entry. Approximately one third of subjects had one or more prior hospitalizations with a primary diagnosis of cardiovascular disease. This is consistent with previous reports of the burden of cardiovascular diseases in patients with COPD. In a cohort of 5,648 patients \( \geq 55 \) years old and receiving a first treatment for COPD, more hospitalizations for cardiovascular diseases than COPD were reported\textsuperscript{74}. Similarly, Curdenkall and colleagues reported that the prevalence of cardiovascular diseases was higher in patients with COPD compared to control subjects, with an increased risk of CVS hospitalization\textsuperscript{75}.

Certain co-morbidities in this patient population are likely under-detected and under-treated, as evidenced by the fact that only 14\% of women and 4\% of men received one or more medications for osteoporosis (calcium, vitamin D or bisphosphonates) in the year before cohort entry. Patients with COPD are at increased risk of osteoporosis because of age, smoking, limited physical activity, and use of glucocorticoids. Chronic systemic inflammation has also been postulated to play a role in the pathophysiology of osteoporosis in these patients\textsuperscript{76,77}. The prevalence of osteoporosis in patients with COPD was examined
in a cross-sectional study of out-patients with severe COPD, aged 50 to 70 years old. Bone density measurements were consistent with osteoporosis or osteopenia in 68% of patients, and X-ray revealed previously undiagnosed vertebral fractures in 25% of participants78. A study of 104 patients hospitalized for COPD revealed a 60% prevalence of osteoporosis79.

Interestingly, a higher proportion of women than men were dispensed benzodiazepines and anti-depressant drugs in the year preceding the index hospitalization. Previous studies have reported a higher prevalence of anxiety and depression among women with COPD. Di Marco et al assessed the prevalence of anxiety and depression in a group of outpatients with COPD and 114 sex- and age-matched controls. Anxiety and depression were frequent in patients with COPD, compared to control subjects, and female patients were found to have higher anxiety and depression, and worse symptom-related quality of life51. In patients with severe emphysema evaluated for lung volume reduction surgery, women were found to report greater breathlessness and depression than men, despite similar health status42. Anxiety has been shown to contribute to the risk of repeat hospitalization in patients with COPD52.

When respiratory medications dispensed in the year prior to the index hospitalization were examined, women received fewer prescriptions for bronchodilators than men. This was particularly notable for prescriptions of ipratropium bromide (Atrovent), while prescriptions for β2-agonists were more comparable. Theophylline prescriptions dispensed were also significantly lower in women. Ipratropium and theophylline are used predominantly for the treatment of COPD. In contrast, β2-agonists are used in the treatment of both asthma and COPD. Inhaled corticosteroids (ICS) prescriptions were also similar in the male and female subjects. ICS constitute first-line therapy for patients with persistent asthma, while their role in the treatment of COPD is more controversial. Certain drugs may have thus been dispensed with different goals in male and female patients. Once again, a component of gender bias in diagnostic labeling and prescription patterns cannot be excluded.
Our findings contrast with those of Dales and colleagues, who examined differences in the clinical expression and management of airway diseases in a primary-care setting\textsuperscript{12}. Despite having a lesser smoking history and better lung function, women were more likely to report breathlessness and to be taking respiratory medications (23.4 of women versus 14.9% of men). Only in the subgroup of patients with severe airflow obstruction was the proportion of men and women taking respiratory medications similar (70% of both men and women). Patients in the present study were selected based on hospitalization for COPD, and are likely to resemble these more severe patients. The similar proportion of men and women dispensed ICS prescriptions in our cohort is consistent with data from the Confronting COPD International Survey, where the likelihood of being treated with an inhaled corticosteroid was not significantly different between men and women\textsuperscript{41}.

Trends in the dispensed prescriptions of respiratory medications were examined to ensure accuracy and completeness of the list of identifier codes used for work with the pharmaceutical database. Between 1990 and 2003, the mean number of $\beta_2$-agonist, ipratropium bromide, inhaled corticosteroid (ICS) and theophylline prescriptions dispensed to men and women in the cohort was charted. The proportion of subjects dispensed $\geq 1$ such prescriptions was also examined. We noted stable trends in the overall number of bronchodilators prescribed to men and women (with decreasing $\beta_2$-agonists and increasing ipratropium bromide), stable ICS use and sharply decreasing theophylline prescriptions. These patterns appear consistent with current clinical practice and COPD guidelines\textsuperscript{1,15}. Trends in baseline medications of patients enrolled in clinical trials from 1987 to 1995 were examined by Van Andel et al\textsuperscript{80}. Over this period, decreasing theophylline use, increasing use of ICS and anticholinergics (ipratropium bromide), and stable use of $\beta$-adrenergics were reported.

Differences in respiratory medications dispensed to men and women could result from differences in disease severity. Because COPD hospitalization was the defining event for cohort entry, moderate to severe impairment can be anticipated among cohort subjects. Given the slowly progressive nature of COPD, it is
unlikely that a large proportion of men or women were asymptomatic in the year preceding cohort entry. The number of prescriptions for respiratory antibiotics and oral corticosteroids dispensed in the year prior to the index hospitalization were examined as markers of disease severity, and were comparable in male and female subjects. This suggests that the index hospitalization successfully resulted in an adjustment of disease severity within our cohort.

The high death rate in both men and women following the index hospitalization further attests to the severity of disease in this cohort. In the first year following cohort entry, 13% of women and 18% of men died. The five-year survival was approximately 55% in women and 45% in men. Vital prognosis after hospitalization for COPD was examined in a sample of patients who had participated in the Copenhagen City Heart Study and were hospitalized for COPD. The crude 5-year survival was 45% (37% for men and 52% for women). One hundred thirty-five consecutive patients hospitalized for COPD were prospectively followed for a median of 838 days by Almagro and colleagues. The mortality at 2 years was 35.6%, with greater mortality observed in women, although there were only 11 female subjects in this cohort.

The most commonly documented cause of death was COPD, accounting for over a third of deaths in both men and women. This may be an underestimate as prior data suggests death in patients with COPD may be attributed to other causes such as CHF or pneumonia. The second most common cause of death in men and women was cardiovascular disease. In their cohort of 135 patients hospitalized for COPD, Almagro et al reported that respiratory disease accounted for 50% of deaths, while cardiovascular disease accounted for 19% of deaths. In contrast, in a cohort of outpatients dispensed a first treatment for COPD, Huiart et al found that cardiovascular disease, and more specifically ischemic heart disease, was reported as a more frequent cause of death than COPD itself. The difference in the present findings is likely attributable to the higher degree of disease severity in a cohort of patients discharged from a COPD hospitalization, leading to COPD being the most common cause of death.
Survival and time to re-hospitalization were compared in male and female subjects, following cohort entry. We chose to examine re-hospitalization for Obstructive Airways Disease (OAD), which encompasses both COPD and asthma hospitalization, to avoid missing repeat hospitalizations in women, who were more likely than men to have been previously hospitalized for asthma. Indeed, repeat hospitalizations with a primary diagnosis of asthma were more frequent among women. The risk of re-hospitalization for either COPD or asthma, however, remained higher for men.

After adjustment for age, prior COPD and asthma hospitalizations, co-morbidities and respiratory medications dispensed, male sex was associated with a 45% increase in the risk of death. The effect of male sex in increasing the risk of repeat hospitalization for OAD was less pronounced, though still significant (Hazard ratio 1.12). In the sample of patients from the Copenhagen City Heart Study who were hospitalized for COPD, Vestbo et al found a significantly higher mortality risk in men, after adjusting for age and FEV181. In contrast, a recent prospective study of patients with COPD referred for long-term oxygen therapy reported a significantly higher risk of death among women, after adjusting for potential confounders14. The reason for these differences in findings is not clear, but likely arises from the selection of a sicker subgroup of patients, requiring long-term oxygen, in the latter study.

Only a small proportion of cohort subjects were hospitalized for COPD prior to the index hospitalization; no impact was detected on survival, but the risk of repeat hospitalization for OAD was significantly increased. Diabetes and cardiovascular disease increased the risk of death and all-cause re-hospitalization. The “protective” effect of diabetes and CVS detected for OAD re-hospitalization is explained by the fact that subjects with these risk factors are more likely to be re-hospitalized for cardiovascular diseases, and while hospitalized these patients are no longer at risk for an OAD hospitalization.

Asthma hospitalization in the year before cohort entry conferred a significantly lower risk of death. This is consistent with the findings of Burrows and colleagues who reported a much better survival in subjects with asthma and
asthmatic bronchitis than in patients with emphysematous COPD. This finding suggests that asthma diagnoses preceding the index hospitalization were mostly valid, or constitute markers of favorable disease features, such as a higher reversibility of airflow obstruction with treatment. The hazard ratio of mortality associated for male versus female gender was recalculated after the exclusion of patients with a prior asthma hospitalization anytime before cohort entry, and was essentially unchanged (HR = 1.43, 95% CI 1.39-1.47). This suggests that the survival advantage of women in this cohort is not simply the result of patients with asthma being mislabeled as COPD.

Patients with asthma and chronic asthmatic bronchitis, in the study by Burrows et al, were mostly female, while patients with emphysema were predominantly male. Recently, sex differences in the manifestations of severe pulmonary emphysema were examined in 1053 patients evaluated for lung volume reduction surgery, as part of the National Emphysema Treatment Trial. Radiographic assessment showed that the proportion of whole-lung emphysema was lower in women, with less peripheral involvement. Histological assessment in a subgroup of 101 patients (41.6% female) revealed anatomically smaller airway lumens with disproportionately thicker airway walls in women. Such gender differences in disease phenotype, if confirmed, may partly explain the significantly lower mortality observed in women compared to men in our cohort. Such an “airway phenotype” in women with COPD may translate into significantly different treatment responses, and this warrants further investigation.
Summary and Conclusions

In a large cohort of elderly patients dispensed respiratory medications used in the treatment of chronic airflow obstruction, and subsequently hospitalized for COPD, we report gender differences in treatment and disease outcome. The cohort consisted of 19,260 women and 23,893 men, with a mean age of 77 years. Women were more likely to have been previously hospitalized for asthma. The prevalence of cardiovascular disease was similar in male and female subjects, but more women received benzodiazepines and antidepressants. In the year preceding the index hospitalization, women were dispensed fewer prescriptions than men for bronchodilators (particularly ipratropium bromide and theophylline), despite similar markers of disease severity. There were 11,245 (58.4%) female and 16,754 (70.1%) male deaths after cohort entry. The five-year survival was approximately 55% for women and 45% for men. COPD was the most frequent cause of death in both men and women, followed by cardiovascular diseases. After adjusting for age, prior COPD and asthma hospitalizations, co-morbidities and respiratory medications dispensed, survival and time to re-hospitalization for COPD or asthma (OAD, Obstructive Airways Disease) were found to be significantly higher in female patients.

Further investigation is required to elucidate the factors that confer a survival advantage to women following a COPD hospitalization. Gender differences in disease phenotype and disease progression warrant further study. Gender dimorphism in COPD was first suggested by Burrows and colleagues in 1987, and may largely explain the differences in outcome we observed. Such gender differences in the clinical expression of COPD have potentially important therapeutic implications. Increasing awareness of the rising prevalence of COPD, particularly in women, combined with greater understanding of differential treatment responses in men and women may lead to more targeted treatment of male and female patients with COPD, while limiting adverse effects.
References


Appendix 1
ICD-9 and ICD-10 codes for COPD hospitalizations

ICD-9 codes for COPD hospitalization

490  Bronchitis, not specified as acute or chronic
491  Chronic bronchitis
492  Emphysema
496  Chronic airway obstruction, not elsewhere classified

ICD-10 codes for COPD hospitalization

J40  Bronchitis, not specified as acute or chronic
J41  Simple and mucopurulent chronic bronchitis
J42  Unspecified chronic bronchitis
J43  Emphysema
J44  Other chronic obstructive pulmonary disease
## Appendix 2
### Definition of co-morbidities

<table>
<thead>
<tr>
<th>Condition</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Oral hypoglycaemic agent, Insulin</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Cardiotropes, Anti-hypertensives, Diuretics, Vasodilators, Anti-platelet agents</td>
</tr>
<tr>
<td>CNS disease</td>
<td>Major tranquilizers, Anticonvulsants, Drugs for parkinsonism, Drugs for Alzheimer’s dementia</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Calcium, Vitamin D, Bisphosphonates</td>
</tr>
<tr>
<td>Rheumatic drugs</td>
<td>Gold salts, Methotrexate, Azathioprine, Chloroquine / hydroxychloroquine, Sulfasalazine</td>
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<tr>
<td>NSAIDS</td>
<td></td>
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<tr>
<td>Benzodiazepines</td>
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<tr>
<td>Anti-depressives</td>
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<tr>
<td>Narcotics</td>
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</tbody>
</table>
Appendix 3

Prescriptions of β2-agonists in the year before t0 from 1990 to 2003

Proportion of subjects prescribed ≥ 1 β2-agonist in the year before t0, from 1990 to 2003
Prescriptions of ipratropium bromide in the year before $t_0$
from 1990 to 2003

Proportion of subjects prescribed $\geq 1$ ipratropium bromide in the year before $t_0$, from 1990 to 2003
Prescriptions of bronchodilators in the year before t0 from 1990 to 2003

Proportion of subjects prescribed ≥ 1 bronchodilator in the year before t0, from 1990 to 2003
Prescriptions of inhaled corticosteroids in the year before t0 from 1990 to 2003

Proportion of subjects prescribed ≥ 1 inhaled corticosteroid in the year before t0, from 1990 to 2003
Prescriptions of theophylline in the year before t0 from 1990 to 2003

Proportion of subjects prescribed ≥ 1 theophylline in the year before t0, from 1990 to 2003