



Women and Chronic Obstructive Pulmonary Disease

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ABSTRACT

Around the world, chronic obstructive pulmonary disease (COPD) is affecting women more than ever before. Increased smoking rates amongst women in the last 60 years, and the continued domestic and occupational exposure of women in low-income countries to biomass fuels and smoke have greatly increased the incidence of COPD in women. COPD presents differently in men and women, and women experience a higher symptom burden, rate of exacerbations and greater risk hospitalization. Additionally, women appear to be more vulnerable to the effects of smoking and develop airways disease at lower doses than men. Despite this, women are often under-represented in clinical trials, very few analyses address sex-specific differences in response to treatment, and management is rarely tailored to the specific needs of women with COPD. This article discusses the evidence and some of the potential approaches to address the burden of COPD in women.

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WOMEN AND COPD

Chronic obstructive pulmonary disease (COPD) is now the third most frequent cause of death in the world, behind ischaemic heart disease and stroke. It will be a major ongoing public health problem for several decades to come due to its increasing international prevalence, ageing populations, continued tobacco smoking and indoor, outdoor and occupational pollution exposure¹. It is becoming clear that COPD affects men and women differently, develops in response to different exposures and doses, and presents clinically in a different way. In the age of precision medicine, it is important to understand these differences in order to address them proactively, and to appreciate that more effective, targeted approaches to prevention and management of COPD in men and women will reduce its burden and impact on health, productivity and mortality.

EPIDEMIOLOGY OF COPD IN WOMEN

Prevalence of COPD in women

The prevalence of COPD in women is lower than in men in most of the studies, but higher than would be expected from tobacco smoke exposure alone. In the international Burden of Obstructive Lung Disease (BOLD) study⁸, using a standardized protocol across 12 sites, the overall prevalence of Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II or higher COPD was 10.1% (standard error [SE] 4.8) overall, 11.8% (7.9) for men, and 8.5% (5.8) for women. The prevalence increased with age, being 7.5% (95% confidence interval [CI] 5.7 to 9.4) among people aged ≥ 40 years and 29.2% (18.1 to 40.2) among people aged ≥ 75 . In relation

to tobacco smoke exposure, site-specific pack-year odds ratios (ORs) varied significantly in women but not in men, suggesting there were several contributors to the risk of COPD in women, apart from tobacco exposure.

COPD prevalence has risen more rapidly in women than men in many high-income countries over the last two decades¹⁻⁶. This reflects increased longevity, improved survival from cardiovascular disease and the change in tobacco smoking uptake that began in the second half of the 20th century, which gradually saw the number of women smoking increase to match male smoking rates, and in some countries, overtake them, even though smoking prevalence overall has fallen⁷. In low- and middle-income countries the prevalence of smoking amongst women is still relatively low compared to males, but women experience many other sources of smoke exposure, greatly increasing their risk of developing COPD.

Mortality in women

Age-adjusted all-cause mortality rates are higher in men than women and this applies also to COPD, even after controlling for COPD severity. In a United Kingdom (UK) study⁸, while COPD prevalence was climbing in women and had plateaued in men, all-cause mortality in people with COPD was higher in men (106.8 versus 82.2 per 1000 person-years) than in women, with a consistently increased relative risk in men of 1.3 even after controlling for the severity of COPD. Significantly increased mortality rates were also observed in adults aged less than 65 years. However, women suffer more morbidity from COPD than men, as will be described below.

Causes of COPD in women: exposure dose and effects differ to men

Women appear to be more susceptible to the effects of cigarette smoke than men, for a given number smoked/day, and total intake⁹⁻¹³ (Fig. 1). There are many possible mechanisms for this, including different molecular and metabolic responses to cigarette and biomass smoke, different airway geometry, patterns of inhalation, intensity and diversity of exposure, and cellular vulnerability¹⁴⁻¹⁸. In a study from Nanjing China exploring the relationship between cigarette smoking and COPD among urban and rural adults > 35 years old, the overall prevalence of diagnosed COPD was significantly higher among men than in women (7.2% versus 4.7%, $p < 0.000$); however, the relationship between prevalence of COPD and total cigarette smoking was dose-dependent by gradient in women, while only men with the highest cigarette smoking rates were more likely to have COPD¹⁹. Similarly, in an analysis²⁰ of the medical records of 844 COPD patients in Finland, women reported significantly fewer pack-years than men. Compared to the men, the women had less advanced airway obstruction, but more severe gas transfer impairment. Parenchymal damage measured by diffusion capacity correlated more strongly with forced expiratory volume in one second (FEV₁) % predicted in women than men. This cohort showed several significant gender-dependent differences in their clinical presentation including having a lower body mass index (BMI), and more psychiatric conditions, especially depression, but men being more likely to have cardiovascular diseases, diabetes and alcoholism.

Multiple studies from different regions of the world have suggested both increased risk and

greater impact of COPD in women who smoke. Two longitudinal Danish studies⁶, the Copenhagen City Heart Study and the Glostrup Population Study combined, found that after adjusting for smoking, women had a 1.5 times greater probability of COPD-related hospitalizations than men, which could not be accounted for by higher rates of hospitalization in women in general. For each pack-year of smoking, women had greater excess loss of FEV₁ in mls per year. In another study, women were disproportionately represented in the subset of patients with COPD with severe disease despite minimal tobacco smoke exposure (defined as < 20 pack-years)⁷. Women were also more likely to present with COPD before the age of 60 years.

Increased susceptibility of women to tobacco and biomass smoke inhalation

In the BOLD study, sex-related differences in smoking patterns (especially in the ever-smoked group) were recorded for almost all sites, and mean pack-years were consistently higher for men than for women. The prevalence of stage II or higher COPD was 10.1% (SE 4.8) overall, 11.8% (7.9) for men, and 8.5% (5.8) for women, but this difference hides the lower exposure to and smoking rates of women, and suggests that factors other than cigarette smoking contribute to COPD prevalence in women.

The recently published study from the UK Biobank¹⁰ confirms these findings of increased susceptibility of women to cigarette smoke. In a very large database of approximately 500,000 subjects aged 40 to 69 years, the association of airflow obstruction and smoking was stronger in women than in men. There was a

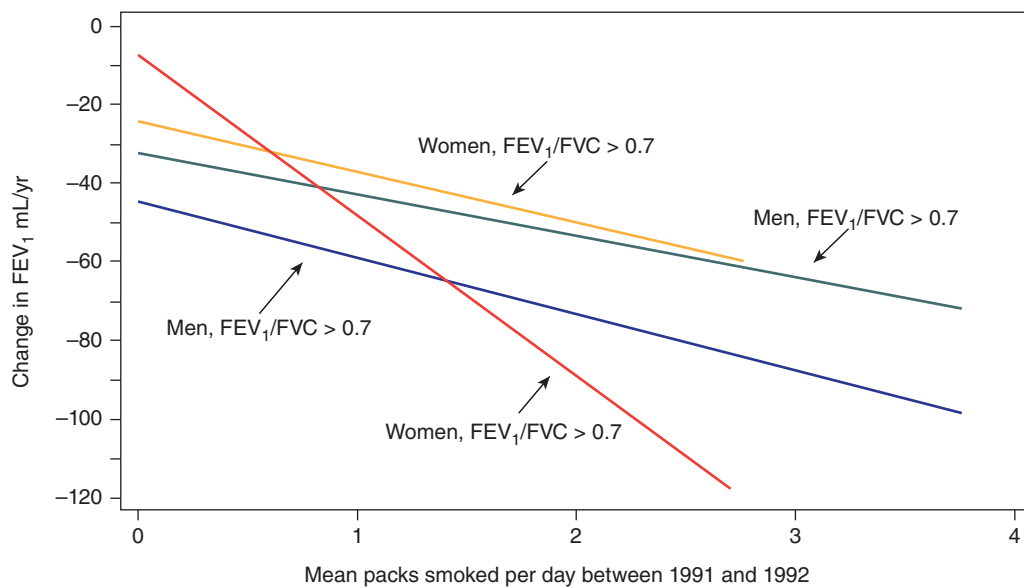


FIGURE 1. Relation between mean packs per day and annual change in FEV₁ in men and women between 1991 and 1992 taken from regression models developed from the Swiss cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SALPADI) (reproduced with permission from Downs SH et al.¹³).

FEV₁: forced expiratory volume in 1 second forced; FVC: forced vital capacity.

greater probability of having airway obstruction with a lower self-reported cigarette smoke exposure among women, and women were at increased risk of airflow obstruction after only 15 years of smoking and five cigarettes per day.

Global smoking patterns are changing and it is estimated that the proportion of women who smoke will rise from approximately 12% in the first decade of this century to 20% by 2025²¹. This will be especially prominent in low- and middle-income regions, while the proportion of women who smoke in high-income regions are expected to progressively fall over the same period. Despite being signatories to the World Health Organization (WHO) Convention on Tobacco Control, many low-middle income countries do not enforce the regulation of tobacco and promotion of tobacco products.

The effects of air pollution consequent on urbanisation and rapid development of many previously predominantly rural countries in Asia, are also likely to have profound impacts on women, both as a synergistic effect with tobacco smoke exposure, and as a direct consequence of airway inflammation secondary to high levels of pollution, although it is not known whether women are more susceptible to atmospheric pollutants from car and diesel emissions¹². Nor has it been proven that outdoor air pollution alone causes obstructive airways disease, although evidence from a number of sources suggest this is likely²²⁻²⁵. Between 2010 and 2025, in the urban population of China alone, prevalent cases of COPD will grow from about 18.5 million to approximately 30 million²⁶⁻²⁸. Around the world, longevity and urbanisation are likely to contribute to an increasing burden of COPD and

costs attributable to work time lost, productivity loss, disability and premature death^{22,23,29-31}.

In low-to-middle income countries, the rise in smoking prevalence in women has been less marked than in high-income countries, however this is changing as young women move to cities, and are exposed to advertising and relatively cheap tobacco. COPD rates in women who are lifelong nonsmokers, are relatively high²⁸⁻³¹. This is a result of multiple different risk factors experienced by women in these countries, including smoke exposure from cooking and heating using biomass fuels, occupational exposures in cottage industries in poorly ventilated workplaces and no protective clothing, and additional, poorly documented exposures such as from wildfires and forest burning^{32,33}. The use of biomass fuel for cooking and smoking is relatively high in many parts of the world³⁴⁻³⁷, and is likely to particularly affect women and children for decades to come, despite vigorous efforts to introduce clean cookstoves and to improve external venting of woodstove smoke using simple flues³⁸⁻⁴⁰. Additionally, it is now understood that there are different trajectories to the development of COPD⁴¹, and early life factors such as premature birth, poor nutrition, smoke and fume exposure and recurrent respiratory infections are risk factors for not achieving predicted normal values for airway function by early adult life^{28,37,42-44}. The sex-related aspects of these have not yet been explored.

Potential explanations for the increased susceptibility of women to smoke exposure

There are many possible contributors to the increased propensity of women to develop COPD

in response to similar or lower exposures than men. The reduced surface area of women's bronchial mucosa, combined with their smaller airways means there is a potentially greater exposure to toxic inhalations and particulates when considered as dose/mm³⁴⁵. There are also important differences between men and women in inhalation pattern, depth, frequency, exhalation and breath hold. Varying sensitivity during different stages of life⁴⁶, or the menstrual cycle may play a role, in addition to important genetic determinants of susceptibility that are only now being identified^{17,18,47}. In the Lung Health Study, female smokers had greater levels of airway hyperresponsiveness and this was higher in continuing smokers than quitters, predisposing women to the increased risk of developing airflow limitation consequent on a combination of airway hyperresponsiveness (AHR) and smoking⁴⁸. However, a great deal more research is needed to understand how sex influences the effects of smoking on airway molecular structures, epithelial inflammation, lung function, severity of emphysema, progression of COPD and the downstream high prevalence of symptoms and risk of exacerbations⁴⁹. Our lack of knowledge in this area will almost certainly have an influence on finding solutions to limit the damage of smoking in women.

The natural history of COPD in women

Women may also experience different trajectories of COPD, especially after ceasing smoking. During three years of the European Respiratory Society's study on chronic obstructive pulmonary disease (EUROSCOP)⁵⁰, in a relatively milder population, there were cross-sectional and longitudinal differences between men and women in symptom prevalence, response to

smoking and treatment. Similar proportions of men and women reported symptoms, although in men better lung function was associated with improvement in wheeze and dyspnoea, and symptom prevalence reduced with annual FEV₁ improvement. The prevalence of phlegm also reduced with budesonide treatment, and was limited to men. Men were also more likely to record an increase in phlegm and wheeze when the number of cigarettes smoked between visits increased. Symptom reporting by men in general appeared to reflect disease activity – either improvement or decline as measured by FEV₁ % predicted. Longitudinally it appeared also that in men particularly, symptoms are a good predictor of disease status, but this was not so evident in women.

In the Lung Health Study, women had more AHR and FEV₁ declined at a similar rate if they continued to smoke, but had a greater improvement in their FEV₁ after smoking cessation and a significantly lower rate of FEV₁ decline than men^{48,51,52}.

SYMPTOM PRESENTATION IN WOMEN

It is now well accepted that men and women respond differently to the presence of symptoms, recommendations for treatment, both prior to diagnosis and when a diagnosis is established^{53,54}. Additionally, there are differences in the frequency of particular COPD phenotypes affecting men and women. Women appear more likely to exhibit small airway disease (bronchiolitis), whereas men are more prone to develop an emphysematous phenotype⁵⁵⁻⁵⁸. It is well recognized that women who develop COPD from biomass exposure are more likely to develop a chronic bronchitic, mucus hypersecretion

phenotype, but in relation to tobacco smoking also, women are more likely to present with airway predominant features^{34,59}, especially chronic bronchitis and wheeze⁶⁰. Women have more severe symptoms when they do have an emphysema phenotype⁴⁹ but in most studies still have a better life expectancy⁶¹.

Missed and mis-diagnosis

Several studies have shown that women are also more likely to be given an asthma diagnosis, even when they have a significant smoking history. This is especially the case in countries where smoking prevalence is traditionally much higher in men, resulting in a higher rate of misdiagnosis in women with COPD compared with men, potentially leading to suboptimal treatment⁶²⁻⁶⁵. In one Canadian study, when spirometry was added, a COPD diagnosis became more probable⁶⁶. Although the gender bias in diagnosis is reduced by the use of spirometry, spirometry in general remains underused, particularly in women⁶³. This is especially so in primary care where most patients receive their initial diagnosis of COPD⁶⁷⁻⁶⁹, giving a higher probability that women will not receive a COPD diagnosis when that is the true nature of their disease.

Prominent airway symptoms, along with a higher prevalence of AHR in women may partly account for this tendency to more readily diagnose asthma than COPD in women⁵¹. A number of investigators have shown that women are more likely to experience delay in the diagnosis of COPD even though they may present earlier⁶⁵. In part, this appears to be a consequence of being more likely to receive an asthma diagnosis than men, even with a similar

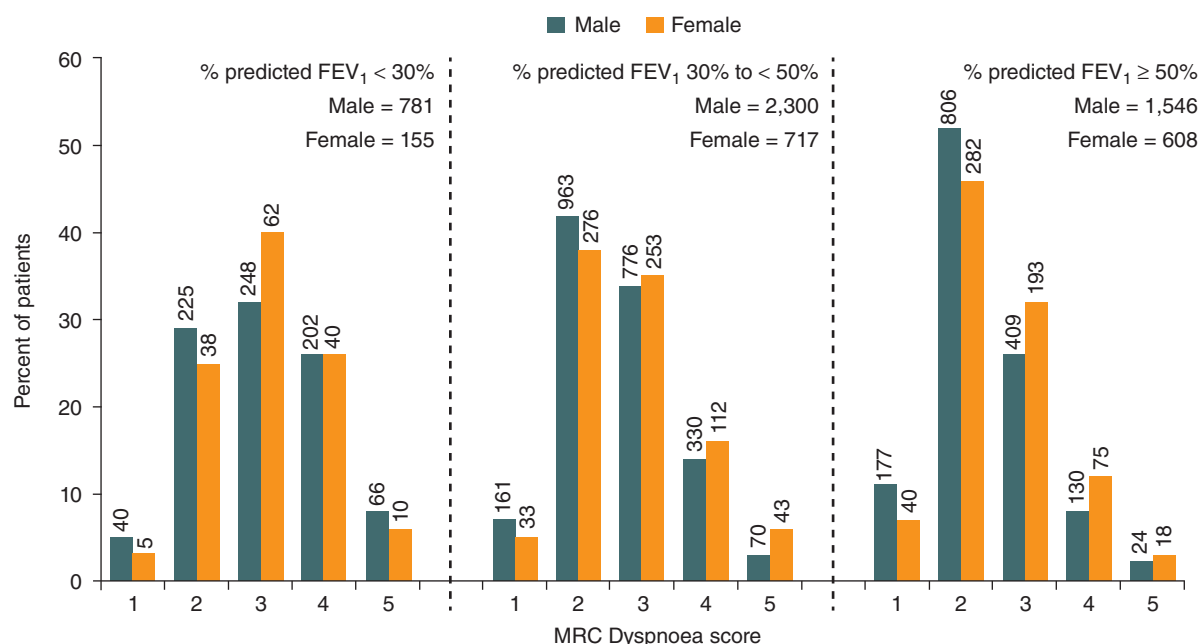


FIGURE 2. Medical Research Council (MRC) Dyspnoea^o scores by sex. In each stage females had worse scores than males ($p < 0.0001$) (reproduced with permission from Celli B et al.⁸⁵).
FEV₁: forced expiratory volume in 1 second forced.

smoking history, when COPD is present. As different treatment strategies are applied to asthma and COPD, and inhaled corticosteroid ICS)-long-acting β_2 -agonist (LABA) is not necessarily the correct treatment for both, it is important that where possible the two diseases are correctly identified and managed.

Women appear to experience different spectrum and severity of symptoms for a given severity of spirometric abnormality. In a Spanish study⁷⁰, women were younger, smoked less, had better PaO₂ and lower PaCO₂, but more exacerbations in the last year and fewer comorbidities however they performed poorer in walking distance, had worse St George's Respiratory Questionnaire (SGRQ) total, symptoms and activity scores, and had a higher degree of

dyspnoea. Comorbidities have been shown to be different in a range of studies, with a greater predominance of anxiety, depression, osteoporosis and sleep disturbance but a lower prevalence of cardiovascular diagnoses^{54,65,71}.

Several studies show that for a similar degree of airway obstruction, women have worse scores on health status questionnaires than men, including for SGRQ domains⁷², and worse dyspnoea scores such as on Medical Research Council (MRC) (Fig. 2). Women may also experience greater psychosocial impairment related to COPD than men⁷³ and have greater levels of anxiety and depression⁷⁴⁻⁷⁸. This aligns with studies demonstrating lower scores in the mental component of the short form (SF)-12 health status questionnaire compared with men⁷¹.

Though women may more frequently report some symptoms such as dyspnoea and wheeze, this is not the case for all symptoms and they may not be as sensitive to change as in men. Women have been noted to be less likely to report phlegm but for a given level of airflow obstruction, experience a greater impact on exercise capacity, breathlessness and quality of life. In a Spanish study⁷⁰, in men and women matched for severity of airflow limitation, women tended to be younger, to have smoked less in total pack years, and have better oxygenation. Despite this they performed less well in walking distance and had worse quality of life scores and a higher degree of dyspnoea at iso-exercise.

In a primary care setting in Canada, the clinical presentation and historical features in ever smokers was assessed by symptom questionnaires and spirometry⁷⁹. Men smoked significantly more than women and were more likely to have an abnormal FEV₁/vital capacity (VC) ratio but more women than men reported breathlessness, a previous diagnosis compatible with airway obstruction and were taking respiratory medications.

Acute exacerbations of COPD

Several studies report a higher rate of exacerbations in women versus men with COPD⁶⁰, although generally women have better short- and long-term survival after severe exacerbations requiring hospitalization^{4,61}. This is despite the fact that mortality rates in many high-income countries are increasing for women and declining for men^{80,81}, and in some, women's COPD-mortality rates are now higher overall⁸². Exacerbation rates and symptom burden have been higher in women recruited into several

large COPD clinical trials as well as in large population cohorts⁶⁰. In the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) cohort, the rate of exacerbations was significantly higher in women than men at each GOLD stage⁸³. In a post-hoc analysis of the Prevention of Exacerbations with Tiotropium in Chronic Obstructive Pulmonary Disease (POET-COPD) trial, the risk of first exacerbation was higher for women compared with men (hazard ratio [HR] 1.31; 95% CI: 1.19-1.43)⁸⁴. In the TOwards a Revolution in COPD Health (TORCH) study, the time to first exacerbation was shorter and the rate of exacerbations was 25% higher in women than in men ($p < 0.001$; 95% CI: 16-34), (Fig. 3), although the number of hospital admissions caused by exacerbations was similar⁸⁵. Although several studies show that women are more likely to be admitted to hospital for an exacerbation⁸⁶ (Fig. 4), they appear less likely to die in hospital⁸⁷. In a population of > 40,000 participants in the Quebec Insurance databases, males had a significantly increased risk of death (adjusted HR 1.45; 95% CI: 1.42- 1.49) and re-hospitalisation for COPD (adjusted HR 1.12; 95% CI: 1.09- 1.15)⁸⁸.

Response to treatment

Smoking cessation is the most important initial step in COPD management. The Lung Health Study suggests that women may benefit more from smoking cessation than men, even though other studies suggest they may have more difficulty giving up^{89,90}. There are no studies designed to examine sex-related differences in the effects of nicotine replacement therapy and smoking cessation medications (such as bupropion and varenicline) appear to be equally effective in men and women^{64,91-93}. As women

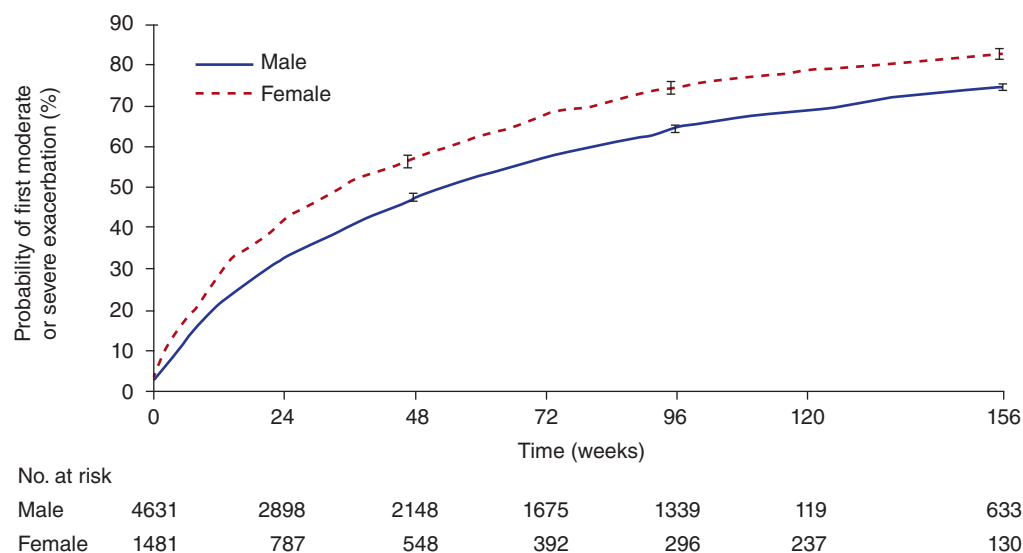


FIGURE 3. Kaplan-Meier graph of time to first moderate to severe exacerbation. Bars are standard errors (*reproduced with permission from Celli B et al.⁸⁵*).

may have greater levels of anxiety and greater smoking dependence than men, they may benefit also from a tailored behavioural approach⁹³. Pulmonary rehabilitation is also a key non-pharmacologic intervention for patients with COPD, but very few studies report any differences between men and women and most enrol more males than females.

In pharmacologic trials, very rarely are gendered analyses undertaken, studies are underpowered for analyses based on sex, particularly when women are underrepresented. In the EUROSCOP study⁵⁰, as already mentioned, the improvement in phlegm on budesonide was limited to men. Longitudinally, men showed a greater response based on their symptom reporting to cigarette exposure (worsening) and treatment (improvement). Women initially reported greater remission of symptoms in the

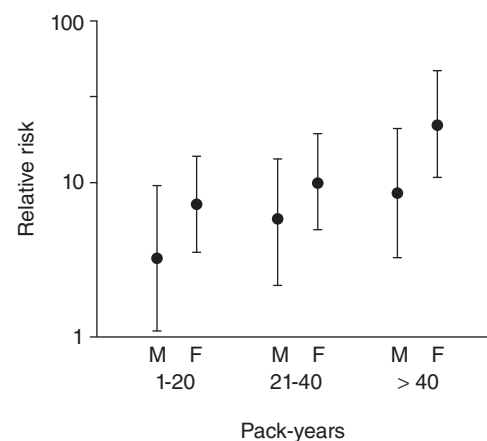


FIGURE 4. Age-adjusted relative risk of hospitalization for chronic obstructive pulmonary disease (COPD) by pack years among smokers who inhaled, in the Copenhagen City Heart Study (CCHS). Lifelong nonsmokers and smokers who did not inhale were used as reference. Note the logarithmic scale (*reproduced with permission from Prescott E et al.⁸⁶*). F: female; M: male.

first year of follow-up but over the three-year period the symptom prevalence differences between men and women disappeared.

Considering the increasing and expansive literature on COPD management, it is lamentable that there are so few studies or analyses of clinical trials to support physicians with gender-focused pharmacological treatment of COPD⁹⁴. Current guidelines are largely based on clinical trials that have recruited many more men than women⁹⁵⁻⁹⁷. The lack of gender-specific recommendations could be because there is no difference in the effectiveness or efficacy of treatments, however, this is not known. Analyses suggest that clinical trials populations differ from real-world patients particularly in gender distribution. As the rate of smoking in women has increased and will inevitably be reflected in increased COPD morbidity and mortality in future decades, there is an urgent need for future trials to redress this imbalance. Further, as many women and children in low-income countries will be exposed to biomass fuels for heating and cooking for decades to come, specific studies examining the effects of treatment in these women with a biomass-chronic bronchitis phenotype of COPD are urgently needed. Randomised controlled trials should adopt strategies to recruit and retain women, and to pre-specify sub-analyses based on gender in order to assess responses to treatment and their determinants. Systematic reviews and meta-analyses, as well as less robust but potentially informative post-hoc analyses should be undertaken to explore gender related treatment effects and to plan future studies. These analyses would be hypothesis generating and would help identify differential effects of treatment and target therapy to reduce the impact of COPD in both men and women.

SUMMARY

There are many differences between men and women in risk factor impact, symptom development, presentation, clinical manifestations and outcomes of COPD. Women's greater risk of developing COPD at lower doses of tobacco, and the continuing exposure of women to biomass cooking and heating fuels in many parts of the world make it probable that globally, women will ultimately have a higher prevalence of COPD than men. In relation to treatment, the differences between men and women's responses have been very inadequately explored, which is of particular concern in view of the increasing prevalence and high symptom burden of disease in women. Research addressing sex-related aspects of COPD is urgently needed. The time is well overdue for a gendered approach to study design and treatment assessment, which would enable us to take a step closer to tailored management of COPD in women.

CONFLICT OF INTEREST

Dr. Christine Jenkins receives honoraria and travel payment to participate on advisory boards and steering committees and to present at educational symposia for several Pharmaceutical companies including AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Med-Immune and Novartis. Her institution receives funding from several companies to undertake clinical research and support fellowships.

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