

Gender differences and chronic obstructive pulmonary disease: an update on the literature

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) has traditionally been viewed as a disease affecting older men with a history of smoking, while being neglected and under-diagnosed in women. This scenario has changed in recent years as there has been a steady increase in COPD prevalence and mortality rates in women. The increased prevalence of COPD among women is likely attributable to several factors including the increased rates of cigarette smoking observed in women during recent years, exposure to indoor air pollution as well as increased occupational exposures since women take on previously male-dominated occupational roles related to risk exposure. In this review we have analyzed the difference in COPD phenotypes and features related to gender difference.

Introduction

A large number of studies report the existence of sex-related (biological, hormonal, genetic) differences and gender-related (environmental, socio-cultural) differences in the manifestations of chronic obstructive pulmonary disease (COPD), including a faster decline in lung function and worse symptoms among females, who also seem to be more susceptible to the toxic effects of cigarette smoke.

The impact of COPD worldwide is expected to increase with a heavy economic burden on individuals and society.

The smoke is the best known etiological factor for this respiratory disease. Reflecting the high prevalence

of smoking among men worldwide, historically COPD was considered to be a disease that mainly affected elderly men.¹ However, in recent years, things have changed and now COPD is a disease that affects women, and in many developed countries, COPD has currently become even more prevalent in women than men.² Furthermore there has been also a steady increase in COPD mortality rates in women. For example, in the year 2000, for the first time in the USA, the number of COPD-associated deaths in women has equaled or surpassed that in men,¹ while in Canada, a longitudinal population study revealed a greater decrease in COPD-related mortality trends in men *versus* women.³ In the European Union from 1994 to 2010, the mortality rate in men decreased from 90.1 to 61.3, but in women, these rates were 27.0 in 1994 and 25.15 in 2010.⁴

The increased prevalence of COPD among women is likely attributable to several factors including the increased rates of cigarette smoking observed in women during recent years, exposure to indoor air pollution (biomass) as well as increased occupational exposures since women take on previously male-dominated occupational roles related to risk exposure.^{3,5} Furthermore, several studies have suggested that women may have an increased susceptibility to the lung-damaging effects of smoking compared with men.^{4,6}

In underdeveloped and developing countries, COPD is still a men's disease and the rate of smoking in women is still less, which is about 10%. However, there have been other noxious sources such as biomass exposure and secondhand smoking that mainly affect women.⁷

These differences between men and women in their susceptibility to COPD risk factors are possibly

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related to biologic and hormonal mechanisms. In addition, there might be clinical differences based on sex. Whilst women are more likely to develop chronic bronchitis, emphysema appears more common among men;⁸ often women complain much dyspnea than men. Exacerbations may result in different outcomes and the treatment adherence may be different according to the sex.⁸ Diagnosis, symptoms, health-related quality of life (HRQoL), co-morbidities, management, natural course, disease progression and mortality could all be influenced by sex, as a result of anatomical and physiological differences between the sexes and cultural and sex-related social factors.^{1,9}

The changing disease paradigm among genders highlights the need for an improved understanding of how COPD affects men and women differently, and how treatments could be optimized accordingly. Understanding physiological differences as well as differences in COPD susceptibility between men and women is important as gender-related differences could contribute to variations in management and effect of the treatment.

In this review, we present and discuss the relationship between COPD and gender differences based on the current literature.

Gender difference in risk factors

Lung and airways development and physiology

Sex hormones affect lung growth and development, airway hyper-responsiveness and detoxification of tobacco smoke. The pubertal switch in asthma from a male-predominant disease to a female-predominant disease may be a manifestation of such effects. Estrogen can induce differentiation and maturation of the lung. It may also be involved in the production of cytokines, triggering a Th2-dominant immune response. Growing evidence indicates that estrogen may delay the loss of lung function, with maintenance of alveolar structure and the number of alveolar attachments to small conducting airways, cilia beat and epithelial nitric oxide.^{10,11} Menopause, which is associated with the decline in estrogen and progesterone, is an important cause of accelerated alveolar loss.¹⁰ In a recent study on biomarkers in COPD, by Torres *et al.*, cytokines such as interleukin 16, pulmonary and activation-regulated chemokine and vascular endothelial growth factor were independently associated with female sex.¹²

Sex differences are also manifested in expression of key genes. For example, surfactant production appears earlier in female than in male neonatal lungs.¹³ This earlier appearance of surfactant in female neonatal lungs favors patency of small airways and

airspace and may contribute to their higher airflow rate and lower airway resistance compared to neonatal males.¹⁴ Consequently neonate males have an elevated risk of developing respiratory distress syndrome (RDS) and dying because of this compared to neonate females.¹⁵ Female lungs tend to be smaller and weigh less than those of males and, on average, may contain fewer respiratory bronchioles at birth.¹⁶ The number of alveoli per unit area and alveolar volume does not differ between boys and girls, but boys have larger lungs than girls.¹⁶ Thus, the total number of alveoli and alveolar surface area are larger for boys than for girls of a given age. Whereas, large airways tend to grow faster than parenchymal tissue in young females, the growth of large airways tends to lag behind that of the parenchyma in young males in a phenomenon known as *dysanaptic growth*, resulting in relatively narrower airways in young males than in young females.¹⁷ During childhood and adolescence maturation of the airways and lungs continues and males continue to have larger lungs than females. Considerable experimental animal data support a role for sex hormones in regulating lung development. Androgens and estrogens have been shown to exert inhibitory and stimulatory effects, respectively on lung surfactant production in a variety of species by a mechanism involving alteration of epidermal growth factor and transforming growth factor- β (TGF- β) signaling events.¹⁸ Adult female mice and rats have more and smaller alveoli than males,¹⁹ thereby providing them with larger alveolar surface area to body mass ratios, whereas adult male mice have larger absolute lung volumes than females but smaller volume to body mass ratios. The formation and maintenance of a full complement of alveoli in females depends on estrogens and has been shown to be mediated in mice by ER α and ER β . Genetic deletion of ER α or ER β decreases the number and increases the size of alveoli in mice, and these changes are more prominent in females than in males.²⁰

Race

About race and gender differences in the effects of smoking on lung function, has been showed that, between 330 COPD patients, Caucasians had less loss of lung function per pack-year smoked than African Americans and men less than women.²¹ Silverman *et al.* found elevated prevalence of COPD (71.4%) in females among the early-onset COPD pro-bands. Female first-degree relatives had significantly lower forced expiratory volume in one second/forced vital capacity (FEV₁/FVC), with greater bronchodilator responsiveness. Female first-degree relatives who smoked had significantly greater risk of FEV₁<40% (odds ratio: 3.56). These results suggest that women may be more susceptible to the development

of severe COPD.²² In the COPD Gene Study, severe early-onset COPD subjects were predominantly female (66%).²³ Subsequently, Jordan *et al.* in their cross-sectional analysis of data from Health Survey for England raised a potential explanation for this controversy. They found that when using the GOLD (Global Initiative for Obstructive Lung Disease), and NICE (National Institute for Health and Clinical Excellence) definitions, women appeared to have a significantly greater susceptibility to COPD for the same level of smoke exposure, but this was not seen when using the lower limit of normal criteria.²⁴

Smoking

The best-known etiological factor for COPD is smoke. While smoking rates in women have largely stabilized in developed countries, the rates continue to increase in developing countries: if effective anti-tobacco initiatives and action plans are not implemented, the prevalence of women smokers is predicted to rise up to 20% by 2025 in these countries. This would mean that there will be 532 million women smokers worldwide by 2025.^{4,25} Men and women may have differential susceptibility to the lung-damaging effects of cigarette smoking; in a large population study, females appear to have more severe COPD with early-onset disease (<60 yr) and a greater susceptibility to COPD with lower tobacco exposure.⁶ Several studies have searched the biological background of possible greater susceptibility to cigarette smoke in women: several etiologies are possible. First, women could be genetically more predisposed to smoking-induced lung damage; second, there might be a greater dose-dependent effect in women smokers. Women have smaller airways than men, so this could cause more exposure with a comparatively smaller amount of smoke.⁴ In a recent mouse model, the excess risk of small airways disease in female mice after chronic smoke exposure was found to be associated with increased oxidative stress and transforming growth factor beta (TGF β 1) signaling, and it is related to the effects of female sex hormones.²⁶ Third, there may be hormonally mediated differences also in tobacco-smoke metabolism.⁴

Exposure to second-hand smoking is another important risk factor. The relative risk for having COPD from second-hand smoking is 1.31 in China, where second-hand smoking has been extremely prevalent. About 49.2% of Chinese non-smokers are exposed at home to second-hand smoking: of those, 51.3% are women and 12.1% are men.

Asthma/chronic obstructive pulmonary disease overlap syndrome

Among adults with COPD, between 13% and 55%

have been reported to also have asthma, termed asthma/COPD overlap syndrome (ACOS), which is characterized by persistent airflow limitation with several features of both asthma and COPD. Some, but not all, studies have reported ACOS to be more common in women; however, no studies have primarily focused on the role of gender in ACOS as compared to asthma or COPD. An Italian study that included an ACOS group²⁷ reported that prevalence of every asthma or COPD was not significantly different by gender.

Infections

Tracheobronchial infections occurred in similar frequency of exacerbations in both men and women. For females the lapse of time between the onset of symptoms and the admission to hospital was much longer.^{1,7}

Occupational and non-occupational exposure

A significant burden of COPD is attributable to non-smoking risk factors, such as occupational exposure, traffic and other outdoor pollution, indoor air pollution, second-hand smoke, outdoor and indoor biomass smoke, dietary factors, chronic asthma and tuberculosis.^{28,29} Epidemiologic studies have shown that 5-12% of subjects with COPD are non-smokers. Biomass smoke contains many harmful pollutants, which can cause acute respiratory infections and chronic respiratory diseases; coal smoke contains sulphur and nitrogen oxides and hydrocarbons that can cause cancer. According to the World Health Organization (WHO), it has been estimated that about 2.4 billion people (about 50% of world's population) and 90% of people living in rural areas use biomass fuel as the primary energy source for domestic purposes:^{30,31} women, spending more time indoors for cooking, are more exposed to biomass fuel combustion products than men.

Another less mentioned possible etiologic factor for COPD is malnutrition. An estimated 20-45% of women of childbearing age in the developing world do not eat the WHO recommended 2250 calories a day. Underweight newborns who are delivered by unhealthy mothers are also at risk. All those factors are mostly related to low socio-economic status associated with poverty, which disproportionately affects women.⁶ Table 1 summarizes the gender differences in risk factors for COPD.

Gender difference in diagnosis

Health care providers are more likely to diagnose COPD in men than women. This has obviously important implications in the care and outcome of these patients.

Although women present with COPD symptoms, they are less likely to receive spirometry.^{4,32,33} In a recent study, which involved 3,500 subjects from Spain, 73% of the patients with spirometric COPD criteria were underdiagnosed, and this percentage was unevenly distributed by sex, being over a quarter times more frequent in women than in men.³⁴ Spirometry can reduce the risk of underdiagnosis and gender bias but data show that only 22% of the physicians request a spirometry.³⁵ In a study of 397 COPD subjects (52% women), self-reported COPD was common among men, and co-diagnosis of COPD with asthma was more common among women ($P>0.05$).³⁶

There may be also a sex disparity in using health resources and patients' perception about their illness and health resource availability. A recent population-based prevalence study found that women were more likely to report COPD diagnostic delay, difficulty reaching their physician and reported that time spent with their physician was insufficient.³⁷ Table 2 highlights gender differences in diagnosis of COPD.

Gender difference in phenotypic manifestations

There are phenotypic differences between women and men in the expression of COPD, as suggested by several studies. A recent USA study showed that

similar numbers of women and men reported dyspnea, but women reported less phlegm and rated their health as poor/very poor.³⁷ NHIS data similarly suggest that chronic bronchitis is more common among women, and emphysema is traditionally more common among men, although since 2011 more women in the US have been diagnosed with emphysema than men.³⁸ In the European Respiratory Society study on COPD (EUROSCOP study), men and women reported similar symptoms; however men had more wintertime phlegm production; symptoms were only correlated with baseline FEV₁ in men but not in women.³⁹ Several studies have shown that women have better functional parameters than men, but even correcting for degree of airflow obstruction, women report more anxiety and depression, worse symptoms (more dyspnea and more exacerbations), lower exercise capacity, more airway hyperresponsiveness, and worse HRQoL than men.^{4,40} Data from the TORCH (Toward a Revolution in COPD Health) study showed that women (n=1481) had higher FEV₁ (47% vs 44% predicted), worse St. George's Respiratory Questionnaire, and worse Medical Council Research Score than men (n=4631). After adjusting for differences in baseline factors, the risk of mortality was 16% higher in men than in women, although this was not statistically significant. Causes of deaths were similar in both sexes; exacerbations were 25% higher in women.⁴⁰ Recent data from Spain showed that

Table 1. Gender difference in risk factors.

1. Sex hormones affect lung growth and development, airway hyper-responsiveness and detoxification of tobacco smoke. Sex hormones affect lung growth and development, airway hyper-responsiveness and detoxification of tobacco smoke. Estrogen can induce differentiation and maturation of the lung. Menopause, which is associated with the decline in estrogen and progesterone, is an important cause of accelerated alveolar loss
2. Men have less loss of lung function per pack-year smoked than women
3. Men and women may have differential susceptibility to the lung-damaging effects of cigarette smoking; females appear to have more severe chronic obstructive pulmonary disease (COPD) with early-onset disease and a greater susceptibility to COPD with lower tobacco exposure
4. Among adults with COPD, about 30% have been reported to have also asthma, termed asthma/COPD overlap syndrome (ACOS), which is characterized by persistent airflow limitation with several features of both asthma and COPD. Some studies have reported ACOS to be more common in women
5. Tracheobronchial infections occurred in similar frequency of exacerbations both in men and women. Females had much longer time from the onset of symptoms
6. A significant burden of COPD is attributable to non-smoking risk factors, such as occupational exposure, traffic and other outdoor pollution, indoor air pollution, second-hand smoke, outdoor and indoor biomass smoke, dietary factors, chronic asthma and tuberculosis. Women, spending more time indoors, are more exposed to biomass fuel combustion products than men

Table 2. Gender difference in diagnosis.

1. Health care providers are more likely to diagnose chronic obstructive pulmonary disease (COPD) in men than women
2. Although women present with COPD symptoms, they are less likely to receive spirometry
3. Self-reported COPD is common among men, and co-diagnosis of COPD with asthma is more common among women

women patients with COPD were significantly younger, had better pulmonary function tests, smoked less but had worse quality of life measured using the EQ-5D and Airways Questionnaire 20 (AQ20), higher anxiety and depression.⁴¹ In a very recent study conducted by Gonzalez in 19,260 women and 23,893 men in Quebec, men had significantly worse survival and significantly increased risk of re-hospitalization for COPD.⁴²

The risk of death in patients with COPD is often graded with the use of a single physiological variable, FEV₁. Recently, in a population of predominantly male patients with COPD a multidimensional evaluation of disease severity and prognosis has been validated: the BODE index (body mass index, degree of airway obstruction, dyspnea and exercise capacity) as a better independent predictor of respiratory and overall mortality than FEV₁.⁴⁰ In 2005 De Torres *et al.* found that men and women with the same FEV₁% show differences in the clinical presentation of the disease; they also found significant differences in all the components of the BODE index; the relative weight of each component of the BODE index differs by gender. Women had worse dyspnea, exercise capacity, and nutritional status at an earlier stage of the disease. Perception of disease and nutritional status has a more important role in women with COPD when a multidimensional evaluation of the disease is performed. The BODE index might be particularly useful in assessing COPD severity in women because it takes into account those aspects of the disease most relevant to this population for a given degree of airflow obstruction.⁴³

Martinez *et al.* examined the computed tomography data from the National Emphysema Treatment Trial: women had less emphysema, smaller airways, and thicker airway walls. Women were younger and exhibited lower body mass index (BMI), shorter smoking history, less severe airflow obstruction, lower carbon monoxide diffusion lung capacity and arterial partial oxygen pressure, higher arterial partial carbon dioxide pressure, shorter 6 minute walk distance, and lower maximal wattage during oxygen-supplemented cycle-ergometer.⁴⁴ Recently COPD Gene Study has investigated if sex-

specific differences in emphysema persists within different subgroups; *i.e.*, i) different GOLD spirometric severity; ii) early-onset COPD (<55 years old); iii) advanced emphysema (>25% emphysema). Compared with females, males had higher emphysema. Females with early-onset COPD, severe emphysema and GOLD grade-IV COPD had similar emphysema as males but markedly fewer pack-years smoking history.⁴⁵

The reasons behind differences in clinical expression of COPD between men and women are likely multifactorial. Patients' response to dyspnea has been affected by their emotional response and interpretation of the dyspneic sensation. Neurobiological studies showed that women had higher intrinsic sensitivity to somatic sensations including dyspnea. Women also demonstrate greater attention to somatic sensations.⁴⁶ Becklake and Kauffmann suggested that societal concepts of athleticism may cause men to report less breathlessness than women;⁴⁷ others have suggested that socio-cultural factors may result in women being less likely to report the production of sputum or phlegm. Some physiologic data suggest that fat-free body mass, which is lower in women with COPD, is related to a lower diffusion capacity and more dyspnea.⁴⁸ In Table 3 are summarized phenotypic differences between women and men in the expression of COPD.

Gender differences in comorbidities

Sex differences in comorbidities are understudied. Many studies found that women were more likely to have depression, anxiety, fatigue, lower BMI and fat-free mass and more exacerbations than men.^{9,40,49,50} The ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) study showed that, in females, cardiovascular comorbidity and diabetes mellitus were less prevalent, whereas osteoporosis, inflammatory bowel disease, reflux and depression were more prevalent.^{50,51} In a Spanish study, instead, females had more heart failure, osteoporosis and diabetes mellitus but less comorbidity compared with men (1.8 vs 3.7); the mean

Table 3. Gender difference in phenotypic manifestations.

1. Similar numbers of women and men have reported dyspnea, but women have reported less phlegm and rated their health as poor/very poor
2. Chronic bronchitis is more common among women, and emphysema is traditionally more common among men
3. Exacerbations are higher in women
4. Women at the same disease severity had less emphysema, smaller airways, and thicker airway walls; moreover, they are younger and exhibit lower body mass index, shorter smoking history, less severe airflow obstruction, lower carbon monoxide diffusion lung capacity and arterial partial oxygen pressure, higher arterial partial carbon dioxide pressure, shorter 6-minute walk distance, and lower maximal wattage during oxygen-supplemented cycle-ergometer

Charlson comorbidity index score was 2.7 and not different between the sexes.⁵² In a Swedish study, men had more lung cancer, ischemic heart disease and renal failure and women had more osteoporosis, hypertension, rheumatoid arthritis, and mental disease.⁵³ A study evaluating sex differences in the prevalence of psychiatric disorders and psychological distress in COPD showed that women had significantly higher anxiety sensitivity and depressive symptoms compared to men, but did not report more limitations in psychological functioning. Women also reported being less confident in their ability to control respiratory symptoms, and more daily physical limitations compared to men, despite having comparable COPD severity, dyspnea scores and exacerbation rates.^{4,44,54} In another study conducted in Italy, women had more anxiety, depression and dyspnea than men.⁵⁵

There are only a few studies conducted on COPD exacerbation, but there might be differences between women and men. The in-hospital mortality due to COPD exacerbation was higher in men of a cross-sectional study utilizing the 1996 Nationwide Inpatient Sample that included 71,130 patients with COPD exacerbations.⁵⁶ Females have more moderate and severe exacerbations, more hospitalization due to exacerbations, and prolonged length of stay for hospitalization.⁵⁷ Probably Table 4 summarizes gender differences in comorbidities of COPD patients.

Gender differences in treatment

Treatment effects and adverse events are not systematically investigated in women and they may be under-treated.

Most studies of pharmacologic agents for COPD have not been designed to assess treatment in men *versus* women and most trials have enrolled more males than females. For example, little is known about how differences in lung anatomy and physiology of males and females may affect dosage, delivery, and effectiveness of inhaled medications. Based on current studies, there is minimal known effect of sex on

efficacy and adverse events of current therapies.⁷ There may also be sex differences in prescribing habits of providers, as well as compliance with medications between men and women. Dales *et al.* found that among patients with mild-to-moderate COPD, the proportion of females on respiratory medications was twice that of males; this difference was not seen in severe COPD.³³

There may also be sex differences in device preferences. Sestini *et al.* found that men were more prescribed *new* dry powder inhalers *versus* metered dose inhalers.⁵⁸ One study found no male/female differences in the efficacy of salmeterol/fluticasone combination therapy on pre-dose FEV₁, exacerbation rate, or QoL scores and there were no differences in adverse events.⁵⁹ Instead another study demonstrated that the effects of tiotropium on lung function, symptoms, and QoL were similar in men and women.⁶⁰ Budesonide led to a reduction in phlegm among men but not women in the Euroscop study.³⁹ The probability of respiratory deterioration (either symptomatic or exacerbations) when stopping inhaled steroids is higher among women than among men.⁶¹ A more recent study evaluated the response of indacaterol/glycopyrronium by sex in patients with COPD: the authors observed that improvements in health status, dyspnea rescue medication use were generally larger in women than in men.⁶²

Certainly, large and better-designed trials are necessary to determine whether clinically meaningful sex differences exist in the pharmacotherapy of COPD.

Smoking cessation

Smoking cessation is the only intervention documented to slow lung-function decline. Women are not only more susceptible to adverse effects of tobacco smoking but also, they may have more benefits upon successfully quitting smoking. This was demonstrated in the Lung Health Study that showed that women who remained nonsmokers had an average improvement in their FEV₁% predicted during the first year that was 2.5 times greater than the

Table 4. Gender differences in comorbidities.

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| 1. In females, cardiovascular comorbidity and diabetes mellitus are less prevalent, whereas osteoporosis, inflammatory bowel disease, reflux and depression are more prevalent |
| 2. Men have more lung cancer, ischemic heart disease and renal failure and women more osteoporosis, hypertension, rheumatoid arthritis, and mental disease |
| 3. Women have significantly higher anxiety sensitivity and depressive symptoms compared to men, but do not report more limitations in psychological functioning |
| 4. Females have more moderate and severe exacerbations, more hospitalization due to exacerbations, and prolonged length of stay for hospitalization |

Table 5. Gender differences in treatment.

1. Women are not only more susceptible to adverse effects of tobacco smoking but they may also have more benefits upon successfully quitting smoking
2. Long-term oxygen therapy (LTOT) improves survival among hypoxemic patients with chronic obstructive pulmonary disease, but the impact of sex on LTOT is not clear
3. Multidisciplinary pulmonary rehabilitation program have showed both in men and women similar improvements in health-related quality of life measures; after 18 months, however, continued benefits were seen in men but not in women
4. Pneumococcal vaccination coverage is higher in men than in women and in subject with high education level

improvement seen in their male counterparts.⁶³ In a recent study Henoch *et al.* have shown that only 34% of currently smoking patients participated in a smoking cessation program and 22% of them in an educational program with women taking part in more than men.⁶⁴ Older pharmacologic therapy with nicotine replacement was more beneficial among men, whereas the newer agents bupropion and varenicline seem to be equally effective in women and men.⁴⁶ Therefore, although women have more difficulties quitting smoke cigarettes, they may have more benefit if they are successful.

Long-term oxygen therapy

Long-term oxygen therapy (LTOT) improves survival among hypoxemic patients with COPD, but the impact of sex on LTOT is not clear. In fact, a meta-analysis showed that women on LTOT had a survival advantage over men,⁶⁵ but, Machado *et al.* reported that survival was significantly worse among women with COPD receiving LTOT.⁶⁶ These discrepancies may be due in part to patient population and analytical approaches, and in part to the criteria for indications to start LTOT.

Pulmonary rehabilitation

A multidisciplinary pulmonary rehabilitation program should be part of the therapy of all patients with COPD, and should include components of exercise training, nutritional counseling, and patient education. Foy *et al.* demonstrated that after 3 months of exercise therapy, both men and women reported similar improvements in HRQoL measures; after 18 months, however, continued benefits were seen in men but not in women.⁶⁷ Moreover Nguyen and coll. in a retrospective study observed significant differences between men and women: women with COPD showed a statistically significant improvement with respect to overall quality of life as measured by St. George's Respiratory Questionnaire and showed significant improvement in their depression score, while only men with COPD showed any improvement in their sleep quality measured by the Pittsburgh Sleep Quality Index.⁶⁸

Vaccination

Influenza and pneumococcal vaccination are recommended in patients with COPD to decrease associated risks at all stages. No correlation was found with age, gender and severity of the disease regarding the coverage rate of both vaccination.⁶⁹ Conversely, pneumococcal coverage in another study was higher in men than in women and in subjects with white-collar occupation and high education level.⁷⁰ Table 5 shows gender differences in the treatment of COPD.

Conclusions

The influence of gender on COPD risk and outcomes is due to a complex combination of both genetic/biophysiological factors and environmental/behavioral factors. Identifying the reasons and mechanisms behind those factors, as well as the sex differences in the pattern of comorbidities, exacerbations, and therapeutic response, may lead to improved therapies and outcomes of COPD's patients.

In our opinion it is necessary that healthcare professionals recognize the gender differences in patients with COPD to develop a more gender-oriented approach towards diagnosis and treatment of COPD and to improve assessment, monitoring and treatment of this disease.

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