

Improving the Management of COPD in Women



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COPD is a highly debilitating disease that represents a substantial and growing health burden in women. There is increasing evidence for sex-related differences in COPD risk, progression, and outcomes. However, the disease receives scant attention as a women's health issue. Thus, a multifaceted approach is required to address COPD in women, including greater awareness, minimization of risk, and further elucidation of the sex-specific factors (biological and cultural) that affect risk, disease progression, and treatment success. This article reviews the current literature on the topic and provides suggestions for achieving better outcomes for the millions of women with COPD worldwide.

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COPD receives scant attention as a women's health issue, despite the fact that women are more likely to die of COPD than of breast and lung cancer combined.¹ The perception that COPD is a disease of older, male smokers is outdated; COPD affects both men and women globally and is particularly prevalent in low- and middle-income countries.² Indeed, the prevalence of COPD globally is increasing more rapidly in women than in men, and the number of female COPD-related deaths now surpasses the number in men in some countries.²⁻⁸ Furthermore, although globally, women are on average expected to live approximately 4.5 years longer than men, the impact of COPD on life expectancy in women may be greater. In addition, mortality rates in

women with COPD are not falling as rapidly as in men.^{9,10}

There is an urgent need to recognize the increasing burden of COPD in women and therefore to facilitate improvements in disease management. Although sex-specific data in COPD studies are scarce, a pattern of relevant sex-specific characteristics is emerging (Fig 1) that warrants awareness and consideration.¹¹ A multifaceted approach is needed, with sustained effort, to achieve the following: reduce the prevalence of COPD by mitigating risk; improve timely diagnosis rates in women by raising awareness of COPD; and improve the management of COPD in women through further sex-specific research and better

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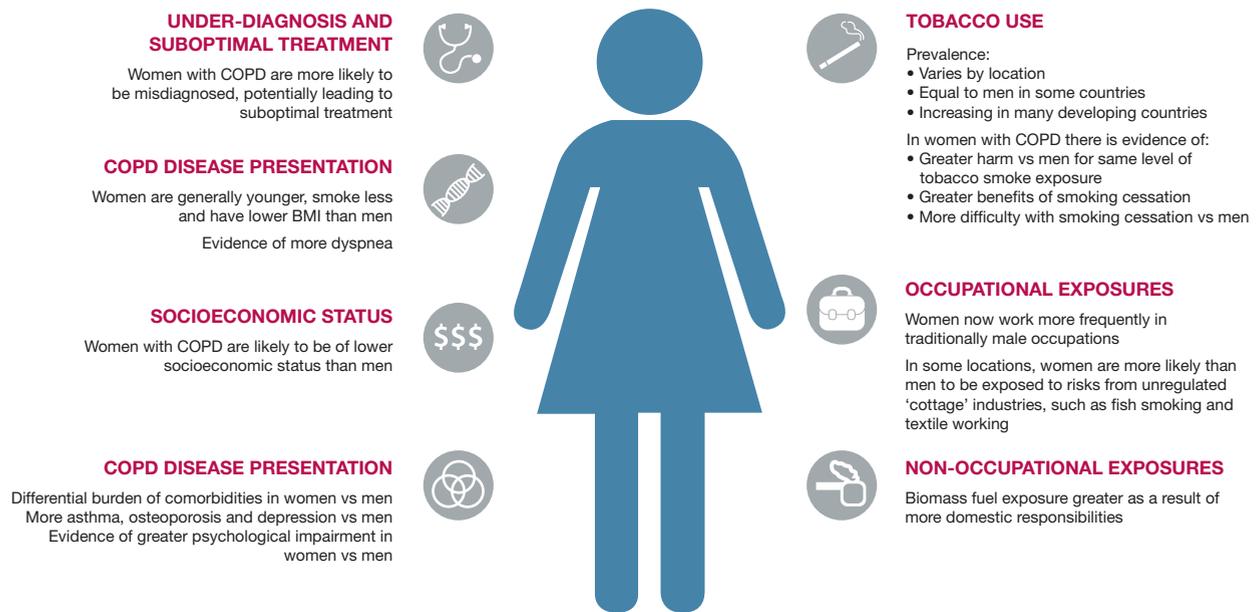


Figure 1 – The impact of female sex on COPD. ^{4,11,20,24,27-30,32,37,38,49-53,55,56,58-61,63,64,67,68,90,91}

consideration of sex-relevant factors, such as common comorbidities. The goal of the present article was to review key data and provide suggestions for achieving these goals.

Search Strategy and Selection Criteria

A PubMed literature search (January 1995-onward) and a search of congress abstracts (2012-January 2015) was performed by using various combinations of the terms “chronic obstructive pulmonary disease,” “COPD,” “emphysema,” “bronchitis,” “women,” and “female”; this search was followed by a manual screening, based on expert opinion, of the results for articles of interest. In addition, we reviewed relevant COPD guidelines and cross-referenced articles of relevance identified by the original search criteria. More than 3,000 publications were retrieved and manually screened for articles of interest.

Risk of Developing COPD in Women

Individual risk for developing COPD is based on both personal susceptibility and environmental risk factors. Although not fully understood, there is indirect evidence suggesting that for a given level of risk exposure, women are more susceptible to developing COPD or have more rapid disease progression than men.^{4,12-19} A study by Sørheim et al¹⁴ found that women were disproportionately represented in the subset of patients with COPD with severe disease despite minimal tobacco smoke exposure (defined as

< 20 pack-years). Women were also more likely to present with COPD before 60 years of age. Similarly, findings from two Danish longitudinal population studies (combined N = 13,897) found that, after adjusting for smoking, women had a greater risk of COPD-related hospitalization compared with men (Fig 2).¹⁶ It is not clear whether these differences in susceptibility are due to differences in genetic predisposition, physical differences (eg, airway and lung size), hormonal influences, or secondhand risk exposure. A recent study

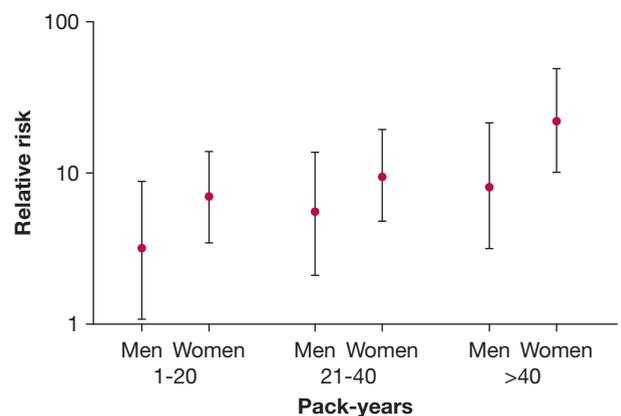


Figure 2 – Age-adjusted relative risk of hospitalization for COPD according to pack-years among smokers who inhaled, in the Copenhagen City Heart Study (n = 9,083). Lifelong nonsmokers and smokers who did not inhale were used as reference.¹⁶ Note the logarithmic scale. (Reproduced with permission of the European Respiratory Society ©. European Respiratory Journal, Apr 1997;10(4):822-827; DOI: [10.1183/09031936.97.10040822](https://doi.org/10.1183/09031936.97.10040822).)

by Hardin et al¹⁵ suggests that there may be variations between different subgroups of female patients that influence susceptibility to parenchymal destruction; however, more research is needed to fully elucidate these and other findings.

Exposure to modifiable risk factors varies significantly according to sex and location, reflecting the social and cultural diversity of different regions. Although it is well established overall that tobacco smoking is the leading cause of COPD in both men and women, the contribution of other factors (eg, occupational and biomass smoke exposure) is important and should be recognized in any initiatives aimed at combating the disease.⁸ An awareness of risk factors other than primary smoking may be of particular relevance to women, who comprise the majority of patients with COPD who have never smoked.^{8,20}

Smoking

It is estimated that, worldwide, the proportion of female subjects in the overall smoking population will rise from approximately 12% in the first decade of this century to 20% by 2025.²¹ A striking increase in female smoking prevalence is particularly apparent in some low- and middle-income regions.^{6,22,23} However, the prevalence of smoking among women varies dramatically by country, ethnicity, and socioeconomic status.²⁰ In a number of countries (particularly high-income countries), smoking prevalence in women has plateaued or decreased.²⁴ Despite this finding, a possible lag time between smoking and onset of COPD means that, even in countries in which COPD has plateaued/decreased in women, the historic trend toward increasing tobacco smoking by women may be reflected in a high COPD burden for some time to come.²⁵

Reasons for smoking may differ between the sexes; female empowerment through tobacco smoking (a phenomenon widely and skillfully promoted by tobacco companies for a number of decades) and weight control are likely to be two reasons for smoking that are more weighted to female subjects than to male subjects.^{21,24,26} In addition, once a smoking habit is established, some evidence suggests that cessation efforts are less successful in women than in men; various contributory factors for this scenario have been suggested that require further study.²⁷ For example, a large, national community study in Canada indicated that women with COPD who smoke have higher rates of nicotine addiction than their male counterparts.²⁷

Although primary smoke exposure is often a focus for prevention campaigns, secondhand smoke exposure may also be a particular concern for women who represent the majority of never-smokers with COPD.²⁰

Biomass Fuel Exposure

Worldwide, approximately 50% of households and 90% of rural households use biomass fuels as their main source of domestic energy.²⁰ As a result, approximately 3 billion people are exposed to smoke from biomass fuel, with women being affected more than men, primarily due to the greater involvement of female subjects in cooking and domestic responsibilities.^{20,28-30} Policies that enable households to move away from a dependence on traditional biomass fuel may help reduce exposure, but in areas where this approach is not possible (ie, where there is no option other than to use cheap fuel), public health initiatives are needed to facilitate the use of flued stoves/chimneys or improved ventilation (eg, through improved house design). Interventions should be of sufficient quality to make the air clean.²⁹

In addition, educational initiatives (particularly for women) highlighting the risks of exposure to indoor air pollution may be useful. It is important to note that COPD in lifelong nonsmokers has also been observed to be sex-specific in developed economies. For example, in the Canadian Cohort Obstructive Lung Disease (CanCOLD) study, exposure to passive smoke and biomass fuel for heating, even in a developed country such as Canada, were independent risk factors for COPD in women.³¹ Reportedly, women exposed to biomass fuels have clinical characteristics and prognosis similar to that of smokers; there are data to suggest, however, that an airway-predominant phenotype may be more common than an emphysema phenotype.^{30,32-35}

Occupational Exposure

The role of the workplace in COPD causation is often underrecognized.³⁶ In women, several different occupational factors may warrant particular consideration in efforts to reduce COPD risk exposure, especially in various cottage industries in low- and middle-income countries. Cottage industries comprise a subgroup of informal, income-generating activities that are often conducted in the home or unregulated environments. Examples include brick making, fish smoking, tobacco curing, and leather working. A significant number of women worldwide are employed by or run cottage industries and, by association, are

exposed to COPD risk factors.³⁷ Steps to educate workers and minimize risk exposure may be useful. In addition, social changes have resulted in women increasingly working in industries that were once dominated by men. Examples include the following: construction; mining; working with leather; manufacture of plastics, rubber, textiles, and food products; spray painting; and welding. These jobs entail subsequent exposure to the associated hazards.³⁸ Occupational health advisors should consider strategies to reduce risk exposure rates, especially in relation to cottage industries.

Low Socioeconomic Status

Having low socioeconomic status and/or living in low- and middle-income countries increases the risk of developing COPD and COPD-associated mortality.³⁹⁻⁴¹ This scenario is of particular relevance for women, who continue to be paid less than men and participate in labor markets on an unequal basis.⁴² Public health strategies and research are needed to address the socioeconomic status disparity between men and women.

Respiratory Infections

Evidence is growing to support the role of respiratory infections in the development, severity, and progression of COPD in both men and women.^{8,43,44} Such findings are of significance in women due to the enormous global health-care burden of respiratory infections in women worldwide.

Hyperresponsiveness

Evidence suggests that the prevalence of airway hyperresponsiveness may be greater in women than in men; hyperresponsiveness is an important predictor of decline in lung function and, possibly, also a greater susceptibility to the effects of smoking in women.^{45,46} Although airway hyperresponsiveness is a hallmark of asthma, which is also more common in women than in men, it frequently occurs in patients with COPD. In addition, asthma and COPD co-exist in some patients, and both conditions may be manifestations of the same basic disease process, as stated in the “Dutch hypothesis.”^{47,48}

Key Suggestions

A multifaceted approach is required to mitigate COPD risk in women, including: educational initiatives (eg, targeted awareness campaigns, pregnancy initiatives, school-aged programs), practical steps to minimize risk

exposure (eg, tailored smoking cessation initiatives, better housing design, occupational protection, respiratory infection risk minimization), political policies (eg, restrictions on smoking in public places, tobacco marketing, cigarette pricing), and better treatment. Initiatives should recognize that the COPD risk factors most commonly experienced by women are not identical to those in men.

COPD Characteristics and Presentation in Women

Although the data are limited, evidence suggests that women with COPD are generally younger, smoke less, have a lower BMI, and are more likely to be of lower socioeconomic status than men.^{11,49-53} In addition, women are more likely to exhibit small airway disease (bronchiolitis), whereas men are prone to develop an emphysematous phenotype.^{15,50,54,55} It has been suggested that biological differences may explain some of the potential differences in disease presentation; women have smaller lumina and disproportionately thicker bronchial walls than men.^{50,55} It is important that physicians are alert to these differences, as a lack of awareness may be associated with delays in disease diagnosis, which are known to have a detrimental impact on patient outcomes.¹¹

Several studies have assessed whether typical COPD symptoms differ by sex. A number of studies have shown similar COPD symptoms between men and women.^{56,57} However, other studies have reported more frequent and/or more severe exacerbations and higher levels of dyspnea in women compared with men.^{28,49,52,55,58-60} Although further studies are required, a higher prevalence of airway hyperresponsiveness in women than men may, at least partially, account for some of the variability between sexes in symptoms such as dyspnea.^{45,46}

The higher rate of exacerbations in women vs men with COPD, identified in some studies, may contribute to the overall higher death rate in women in some countries, such as the United States.^{28,49,55,59} In the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) COPD cohort (n = 2,164), the rate of exacerbations was found to be significantly higher in women than in men at each Global Initiative for Chronic Obstructive Lung Disease stage.⁵⁸ Similarly, in a post hoc analysis from 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: 1.31 [95% CI: 1.19-1.43]).⁵⁹ Data from the Towards a Revolution in COPD Health (TORCH) study also showed that the time to first exacerbation was shorter and the rate of exacerbations was 25% higher in women than in men ($P < .001$; 95% CI: 16-34) (Fig 3), although the number of hospital admissions caused by exacerbations was similar in both sexes.⁴⁹

Altogether, differences in dyspnea and BMI contribute to poorer prognostic scores (eg, the Body-mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index) in women compared with men who are matched for lung function and age.⁵² These findings warrant further investigation, including the effect of these sex-related differences on treatment and the utilization of health-care resources by women.

Key Suggestions

Further research is needed to fully understand sex differences in COPD symptoms and presentation. Physicians should be aware of likely differences, such as younger age of presentation and lower rates of primary smoking.

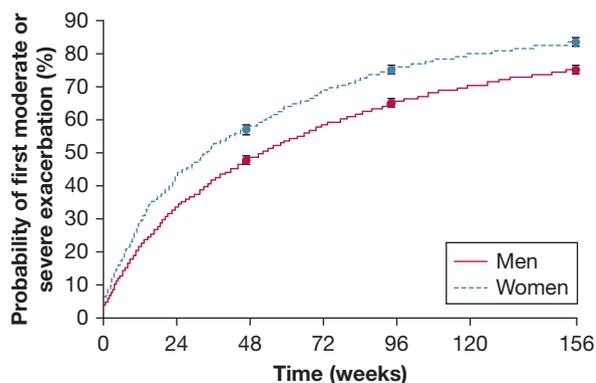


Figure 3 – Kaplan-Meier graph of time to first moderate to severe exacerbation in the Towards a Revolution in COPD Health (TORCH) study ($n = 1,481$ women; $n = 4,631$ men).⁴⁹ Bars represent SE. (Reprinted with permission of the American Thoracic Society. Copyright © 2016 American Thoracic Society. Celli B, Vestbo J, Jenkins CR, Jones PW, Ferguson GT, Calverley PM, Yates JC, Anderson JA, Willits LR, Wise RA; Investigators of the TORCH Study. Sex differences in mortality and clinical expressions of patients with chronic obstructive pulmonary disease. *The TORCH experience. Am J Respir Crit Care Med.* 2011;183(3):317-322. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.)

Interactions Between Women With COPD and Health-care Providers

Women with COPD are likely to have more frequent interactions with health-care providers and use more health-care resources than men.^{13,58,61,62} However, there remains a “male dominated” bias in physicians’ awareness of COPD, which results in a higher rate of misdiagnosis or delayed-diagnosis in women with COPD compared with men, potentially leading to suboptimal treatment.^{4,11,63,64} Although the sex bias in diagnosis is reduced by the use of spirometry, this test in general remains underused, particularly in women.⁶³

There is some evidence to suggest that there may be differences in men and women’s perception of the COPD care they receive.⁶⁴ In addition, coping strategies may differ between men and women.⁶⁵ Further research in this area is needed to determine how women with COPD can best be supported.

Key Suggestions

It is important for the health-care community to address the sex bias that exists in the diagnosis of COPD. Strategies include prompt use of spirometry and careful history-taking to identify and quantify exposure risk. Further research is needed to identify the factors influencing attitudes and coping strategies for women with COPD to enable improvements in care.

Focusing on the Patient: How Does COPD Affect Women?

A majority of available studies have identified poorer health status and quality of life (perceived and actual) in women compared with men, although this finding is not universal.^{50,58,60,62,66,67} A study of 90 patients with COPD found that, for a similar degree of airway obstruction, women presented with a greater impairment in health status than men for all domains of the St George’s Respiratory Questionnaire (Fig 4).⁶² Worse health status in women was also found in a study of 10,711 patients with COPD who smoked, as evidenced by their mainly lower scores in the mental component of the 12-item Short-form Health Survey compared with scores of corresponding male patients.⁶⁷ Furthermore, older women may experience greater psychosocial impairment related to COPD than men.⁶⁸ Anxiety and depression contribute to the substantial burden of COPD-related morbidity and are associated with more impaired quality of life and reduced adherence to treatment.^{69,70} Women with COPD report higher levels of anxiety and depression than men with

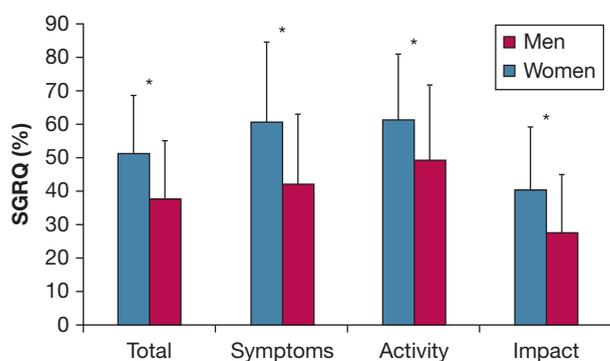


Figure 4 – Mean St George's Respiratory Questionnaire (SGRQ) scores according to sex ($P < .05$) in a study that included 90 patients with COPD (60 male subjects and 30 female subjects; mean age: 64 ± 9 years) with a wide range of airway obstruction disorders (mean FEV₁: $56\% \pm 19\%$ of predicted).⁶² (Reproduced under Creative Commons license CC BY-NC from Ferrari R, Tanni SE, Lucheta PA, Faganello MM, do Amaral RA, Godoy I. [Gender differences in predictors of health status in patients with COPD]. *J Bras Pneumol.* 2010;36(1):37-43.)

COPD, furthering the burden of COPD in women.^{56,66,71-73}

COPD exacerbations are associated with morbidity, mortality, resource burden, and health-care costs. Even after an exacerbation resolves, respiratory, physical, social, and emotional impairments may persist for a prolonged period of time. Although rates of exacerbations may be higher in women (see earlier discussion), some evidence suggests that outcomes following an acute exacerbation may be better in women than in men.^{65,74}

The impact of higher levels of dyspnea, occurring at earlier disease stages in women vs men, is important.^{49,75} Further research is needed to fully elucidate the reasons underlying these differences,⁷⁵ which may be related to differential exposure to risk factors such as biomass fuels and tobacco exposure,^{75,76} as well as different thresholds of symptom awareness and reporting for men and women.

Key Suggestions

There is some evidence suggesting sex-related differences in the impact of COPD, but further research is needed to explore more extensively the influence of sex on COPD disease indicators, such as quality of life and exacerbations, to facilitate tailored intervention programs.

Evidence for Treating Women With COPD

The treatment of COPD involves a range of interventions (pharmacologic and nonpharmacologic).

Where applicable, smoking cessation is an important component of COPD intervention and may result in even greater benefits in women compared with men. Results from the Lung Health Study ($n = 3,348$ men; $n = 1,998$ women) showed that the improvement in FEV₁% predicted was 2.3 times greater in women than in men in the first year of smoking cessation.⁷⁷ Unfortunately, women may be less successful with long-term smoking cessation than men,²⁷ especially with nicotine replacement therapy, although some smoking cessation agents (eg, bupropion, varenicline) seem to be equally effective in men and women.^{4,6,13,78} The fact that women seem to have a greater behavioral dependence than men emphasizes the need for a tailored behavioral approach.¹³

There is a distinct lack of evidence from clinical trials to support physicians and the use of sex-focused pharmacologic treatment of COPD.⁷⁹ Current guidelines are largely based on clinical trials that have recruited many more men than women.^{8,80,81} The lack of sex-specific recommendations could be because there is no difference in the effectiveness or efficacy of treatments; however, whether this assumption is true is unknown. Analyses suggest that clinical trial populations differ from real-world patients, particularly in sex distribution.⁸² There is a need for future trials to include more female participants and to prespecify subanalyses on the basis of sex to study whether biological differences affect the way women respond to medications and therapeutic strategies.⁸² In addition, studies should consider the use of sex as a variable in its own right.⁷⁹

The lack of current evidence represents, in the view of the authors, a missed opportunity, as most large randomized controlled trials could provide valuable data on the impact of sex. Furthermore, although not as robust as prespecified analyses, the opportunity exists to perform post hoc analyses on available datasets and pooled datasets from existing randomized controlled trials. Such analyses would significantly increase the number of women analyzed and may provide powerful findings.

On theoretical grounds, there are good reasons to tailor the medications prescribed for COPD to account for sex. For instance, women are generally more prone than men to develop osteoporosis and are more likely to develop it at an earlier age. Therefore, high-dose inhaled corticosteroids could be relatively more detrimental in women than in men.⁸³ Women receiving inhaled

TABLE 1] Summary of Key Potential Differences in COPD Features Between Women and Men, With Authors' Opinion of the Strength of Evidence Supporting These Differences

Key Potential Differences in COPD Features Between Women and Men	Supporting References	Authors' Opinion on Strength of Evidence (A, B, C, or D)	Requirement for Further Research	Implications
Disease susceptibility				
Women are more susceptible to COPD for a given level of risk exposure	12, 14, 15, 18	B	Yes	<ul style="list-style-type: none"> • A multifaceted approach is required to mitigate COPD risk in women, which recognizes the potential for greater risk
Risk factor exposure differs between sexes	28-30	A	Yes	<ul style="list-style-type: none"> • Practical steps to minimize risk exposure should be sex-specific and consider factors other than smoking (although it is recognized that smoking is a primary causative factor of COPD in men and women)
Reasons for smoking differ between sexes	26	B	Yes	<ul style="list-style-type: none"> • Sex-specific smoking strategies should be implemented
Disease presentation				
Women with COPD are generally younger, smoke less, have a lower BMI, and are more likely to be of lower socioeconomic status than men	11, 49-53	B	Yes	<ul style="list-style-type: none"> • It is important that physicians are alert to potential differences in disease presentation • A lack of awareness may be associated with delays in disease diagnosis
Women appear more likely to exhibit small airway disease (bronchiolitis), whereas men are prone to develop an emphysematous phenotype	15, 50, 54, 55	C	Yes	<ul style="list-style-type: none"> • It is important that physicians are alert to potential differences in disease presentation • A lack of awareness may be associated with delays in disease diagnosis
Symptoms				
Women with COPD have more severe exacerbations and higher levels of dyspnea than men	28, 49, 52, 55, 58-60	C	Yes	<ul style="list-style-type: none"> • Further research is needed to fully understand the sex differences in COPD symptoms • Physicians should recognize the potentially high symptom burden of COPD in women and treat accordingly
Prevalence of hyperresponsiveness is greater in women than in men	45	B	Yes	
Comorbidities				
Women seem to have greater susceptibility to asthma, osteoporosis, anxiety, and depression but appear less likely to have cardiovascular disease	32, 52, 56, 60, 61, 67	C	Yes	<ul style="list-style-type: none"> • Physicians should be aware of and optimize the treatment of comorbidities in women with COPD • Care should be taken when selecting COPD treatments to ensure that the chosen therapy does not negatively affect comorbidities

(Continued)

TABLE 1] (Continued)

Key Potential Differences in COPD Features Between Women and Men	Supporting References	Authors' Opinion on Strength of Evidence (A, B, C, or D)	Requirement for Further Research	Implications
Health status and quality of life				
Health status and quality of life is lower in women than in men with COPD	50, 58, 60, 62, 66, 67	C	Yes	<ul style="list-style-type: none"> Further research is needed to explore more extensively the influence of sex on quality of life, to facilitate tailored intervention programs
Pharmacologic and nonpharmacologic intervention response				
Women may be less successful with long-term smoking cessation than men	27	B	Yes	<ul style="list-style-type: none"> The potential need for sex-specific smoking cessation initiatives should be recognized
Smoking cessation may be associated with greater benefits in women vs men	77	C	Yes	<ul style="list-style-type: none"> Physicians should be aware of the benefits of smoking cessation for women with COPD
The benefit of pulmonary rehabilitation may differ between sexes	85, 86	C	Yes	<ul style="list-style-type: none"> Further research is needed
Sex-specific differences in response to pharmacologic therapies are possible	Not applicable	D	Yes	<ul style="list-style-type: none"> Studies should consider the use of sex as a variable in its own right

Grading (adapted from the GRADE classification system⁹²): A, several high-quality studies with consistent results; B, several well-performed observational studies (dealing appropriately with selection, observation/measurement, and confounding biases); C, fewer well-performed observational studies (some biases, unlikely to compromise the findings in a major way); and D, no study or studies with major flaws.

corticosteroids should have their bone mineral density monitored and be prescribed vitamin D, calcium, and treatments for osteoporosis, where appropriate.

Differences between sexes in ability and adherence to treatment warrant consideration. For example, some evidence highlights potential differences in inhaler technique between sexes, with women experiencing greater difficulties; however, such findings require further study.⁸⁴

A multidisciplinary pulmonary rehabilitation program should form an important component of COPD therapy for all patients and should include exercise, nutritional counseling, and patient education.⁶ However, data concerning the impact of sex on the effects of pulmonary rehabilitation are scarce. Some evidence suggests that women and men may differ in their response to pulmonary rehabilitation, but this finding is not universal, and more research is needed.⁸⁵⁻⁸⁸

In addition to interventions directly targeting COPD, recognition and treatment of relevant comorbidities are important. COPD often coexists with other diseases,

and the presence of comorbidities can detrimentally impact health status, COPD progression, and outcomes. A number of studies have shown a higher burden of comorbidities in women compared with men.^{28,32,58,61} In particular, women seem to have greater susceptibility to asthma, osteoporosis, anxiety, and depression but are less likely to have cardiovascular disease.^{32,52,56,60,61,67} It should also be recognized that more women than men experience overlap between asthma and COPD, which may result in a higher overall health-care burden than the separate components alone.⁸⁹ Care should be taken when selecting COPD treatments to ensure that the chosen therapy does not negatively affect comorbidities.

Key Suggestions

More clinical data are needed on the sex-specific effects of various interventions and sex-specific differences in response to treatment. Post hoc analyses of data from completed randomized controlled trials and pooled databases would provide useful insights into sex-specific

treatment responses. Clear guidance is needed to enable physicians to better recognize and treat comorbidities in women with COPD.

Summary and Future Focus

There is clearly an urgent need to both raise levels of awareness of COPD in women and to implement more successful strategies for the prevention and treatment of COPD in women. When formulating these strategies, the inherent differences between COPD in men and women (biological and cultural) and the practical consequences of these differences should be considered (summarized in Table 1). A multifaceted approach encapsulating policy makers, the research community, health-care providers, employers, women, and caregivers is required that examines risk (primary and secondary) avoidance strategies. Better awareness within the health-care community of the increasing burden of COPD in women is important to improve disease diagnosis and treatment. A tailored pharmaceutical approach based on the sex-specific differences in symptoms and health status is needed moving forward. The availability of education programs for women with COPD and their families would empower patients to manage their disease more effectively.

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