



## Women and COPD do we need more evidence?

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# Women and COPD: do we need more evidence?

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**The face of COPD is increasingly female. We need more evidence and a change in how the disease is managed.** <http://ow.ly/zueL30mWqlS>

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**ABSTRACT** The increasingly female face of chronic obstructive pulmonary disease (COPD) prevalence among women has equalled that of men since 2008, due in part to increased tobacco use among women worldwide and exposure to biomass fuels. This finding is supported by a number of characteristics. There is evidence of susceptibility to smoking and other airborne contaminants, along with epidemiological and phenotypic manifestations. COPD has thus become the leading cause of death in women in the USA. The clinical presentation is characterised by increasingly pronounced dyspnoea with a marked tendency towards anxiety and depression, undernutrition, nonsmall cell lung cancer (especially adenocarcinoma) and osteoporosis. Quality of life is also more significantly impacted. The theories advanced to explain these differences involve the role played by oestrogens, impaired gas exchange in the lungs and smoking habits. While these differences require appropriate therapeutic responses (smoking cessation, pulmonary rehabilitation, long-term oxygen therapy), barriers to the treatment of women with COPD include greater under-diagnosis than in men, fewer spirometry tests and medical consultations. Faced with this serious public health problem, we need to update and adapt our knowledge to the epidemiological changes.

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## Introduction

Chronic obstructive pulmonary disease (COPD) is no longer a respiratory disease that predominantly affects men, and less still the elderly. It encompasses several phenotypes and a specific female phenotype cannot be ruled out.

There is a significant delay in diagnosis because women do not seek medical attention for dyspnoea but for fatigue, resulting in major psychosocial consequences and impaired quality of life [1]. The experience of this disease is difficult for these women because COPD is an invisible disease that can cause misunderstanding among family and friends.

In the USA, COPD is the leading cause of death among female smokers [2, 3], ahead of lung cancer and cardiovascular diseases. Under-diagnosis in primary care medicine is still common [4] because the medical profession needs to change its perception and teaching of COPD as a male disease, a misperception that has stuck with them since their early years of medical school. COPD has female-specific clinical manifestations and comorbidities.

The Fletcher curve is still used today to plot the rate of forced expiratory volume in 1 s (FEV<sub>1</sub>) decline, despite only male patients being used and despite the identified decline in females [5, 6].

## The rise of smoking among women

Catherine de Medici was the first woman in French history to use tobacco, yet consumption by women would long remain marginal. A whiff of scandal surrounded female smokers such as Georges Sand, who would visit literary salons with a pipe or cigar. Not until the 20th century did cigarettes become widespread among women. Female smoking trends rose in tandem with the changing status of women.

Smoking trends among women seem to follow the same pattern as the trend in male smoking after a lag of nearly a century [7]; smoking first started among the upper classes and then spread to working-class men, who became the primary tobacco users. This trend went hand-in-hand with a sharp increase in the number of smokers. It is now thought that smoking among men has reached its peak and is sociologically in decline. For women, this trend began in the interwar years. By smoking, women signified their membership of a privileged social group and their desire for emancipation. This was the fashion statement of the flappers. Between 1950 and 1970, cigarettes permeated every stratum of society and became commonplace.

The phenomenon was aided by advertising [8]. The tobacco industry sought to portray cigarettes as a means of seduction, first by lauding the slimming effects of tobacco and then by filming glamorous actresses like Marlene Dietrich. Many American actresses signed up to these manipulative practices, and their European counterparts followed suit soon after.

However, an encouraging trend is emerging from the West: in the USA, smoking among women is viewed negatively and its harmful health consequences are recognised. Sociologically, it is in decline. And now, Europe seems to be catching up. We can expect a more rapid rate of decline in smoking prevalence among women than among men.

Confronted by this risk of declining tobacco use in Europe, the tobacco industry is looking elsewhere for market share. It has shifted its interest to developing countries, where it is still possible to win over large numbers of new consumers and where smoking prevention measures are underdeveloped. In these countries, women and young people are prime targets. A report by the World Health Organization (WHO) also points to evidence that tobacco advertising increasingly targets young girls [9]. The messages conveyed by advertising are identical to those which have been tried and tested in Western countries; emphasis is placed on the social acceptability of women who smoke and on smoking as a sign of emancipation. An article by HITCHMAN and FONG [10] shows that there is a close correlation between female and male smoking rates and female empowerment. This correlation is clearly associated with the level of economic development. Will the trend towards greater female empowerment also lead to a tobacco epidemic among women [10]? To highlight the significance of the risk posed by rising tobacco use among women worldwide, the theme for the World No Tobacco Day organised by WHO in 2010 was "Gender and tobacco with an emphasis on marketing to women".

Yet the increase in female smoking is not necessarily inevitable. During the 20th century, the prevalence of female smoking declined in China. The smoking rate among women was 25% at the start of the century and increased further in the 1930s, but then experienced a decline in the second half of the 20th century. This reversal coincided with the emergence of new sociocultural norms which frowned on smoking among women. These new norms were conveyed through movements based on traditional values extolling behaviours that promoted a healthier mind and body [11]. The Global Adult Tobacco Survey (GATS) was conducted by the WHO to assess household tobacco consumption in different countries around the world.

In 2010, it was conducted among Chinese households. It showed that 52.9% of men were reported to smoke while only 2.4% of women smoked [12].

### Epidemiology of COPD in women

COPD remains under-diagnosed, especially in women [13]. Two studies carried out in North America and Spain show similar results. Female smokers who visit a physician are more than one-third less likely to be diagnosed with COPD than male smokers. Spirometry testing and referral to a pulmonologist are less common for women [4, 14, 15]. Women reportedly suffer a delay in the diagnosis of COPD, explainable in part by voluntary postponement of access to a consultation or in some patients by the prevalence of symptoms of fatigue or depression that point to a different type of treatment [16]. Allowing for these reservations, the prevalence of COPD is currently estimated, depending on the country, to range from 4.5% to 10.2% [17, 18]. Although a 2006 meta-analysis assessed prevalence at 9.8% among men and 5.6% among women [19], the latest data mitigate this difference. The Burden of Obstructive Lung Disease (BOLD) study, in which prevalence was found to be 11.8% among men and 8.5% among women, reports a higher prevalence at the moderate stages among women in the USA, Austria, Iceland and Australia [20]. In 2008, the WHO estimated that 168 million men and 160 million women were affected worldwide [21]. An analysis of data from 1998 to 2009 shows that the prevalence of COPD in the USA increased in women and decreased in men. The same trends were found in Canada, the Netherlands and Austria [22–24]. In the USA, the number of women diagnosed with emphysema has outnumbered that of men since 2011 [24]. An increase in smoking among women in all countries, including France, has been observed in parallel with the exposure of women to indoor smoke as a result of burning biomass fuels in developing countries [25–28]. Women are more susceptible to tobacco, having a more severe disease despite lower cumulative tobacco consumption, earlier onset of COPD, and faster decline in FEV<sub>1</sub>, but conversely obtain greater benefit from cessation of exposure [24, 29]. This susceptibility to airborne contaminants involves not only tobacco. CELLI *et al.* [30] found that 80% of nonsmoker COPD patients are women, probably on account of exposure to biomass fuels.

In Spain, the ECCO study evaluated the comorbidity in COPD patients hospitalised in internal medicine departments. The mean number of comorbidities was 3.7 in men and 1.8 in women ( $p < 0.05$ ). Women had a lower prevalence of ischaemic heart disease and alcoholism, but presented more frequently with heart failure, osteoporosis and diabetes [31]. In a recent Swedish study of oxygen-dependent COPD patients, women had significantly higher hypertension, higher rates of depression and higher rates of osteoporosis. The presence of a comorbidity was an independent predictor of mortality and the effect was similar for both sexes; nevertheless, mortality was lower among women [32, 33]. Several authors have found a higher frequency of depression in women and a greater impact on quality of life [34]. Dyspnoea appears strongly associated with depression in women [34–37]. In France, a working group studying a real-life COPD patient population showed that, for a given age and level of airflow obstruction, women have a higher BODE index (body mass index, airflow obstruction, dyspnoea and exercise capacity) due to a lower body mass index and more pronounced dyspnoea, suggesting a poorer overall prognosis [38]. Considering the pulmonary hypertension phenotype in COPD, it is equally present in both sexes as shown by the ASPIRE register, whereas there is a female predominance in pulmonary hypertension in group one [39].

Between 1990 and 2010, COPD became the third leading cause of death in the USA. The COPD mortality rate declined among men in the USA between 1999 (57.0 per 100 000) and 2006 (46.4 per 100 000), whereas there was no significant change in mortality rates for women (35.3 per 100 000 in 1999 and 34.2 per 100 000 in 2006). In 2000, the number of women dying from COPD surpassed the number of men [40]. A recent assessment of mortality rates due to COPD in the cohorts from the National Health and Nutrition Examination Survey (NHANES) I and NHANES III in the USA showed a smaller decrease in the mortality rate among women with moderate or severe COPD than among men (3.0% *versus* 17.8%) [41]. Thus, the survival advantage of women with COPD has been diminishing [3].

### Is there a specific COPD-related phenotype in women?

Women with COPD appear to have a different clinico-radiological phenotype from that of men. In smoking- or FEV<sub>1</sub>-matched men and women, women present with more symptoms such as dyspnoea [42, 43] or cough [14]. Even if they produce less sputum than men [14, 44], they are more likely to have a chronic bronchitic phenotype. This seems to confirm the histopathological analyses [42]; although women have less severe COPD than men, they have thicker small airway walls (<2 mm in tissue removed during lung volume reduction surgery). Conversely, a computed tomography analysis showed thicker bronchial walls in men [45]. The significance of emphysema in women is also under discussion [19]. In the National Emphysema Treatment Trial (NETT) study of patients with severe COPD before lung volume reduction surgery [42] or in a lung cancer screening study [46], smoking-matched women had less emphysema than men. Women presenting with the same airflow obstruction and lower smoking rates are usually younger

and have more frequent exacerbations [47]. This susceptibility to tobacco smoke in women favours a faster rate of FEV<sub>1</sub> decline [48–51].

Several cohort studies of patients in the Genetic Epidemiology of COPD (COPD Gene) study support the existence of a sex-related genetic component in COPD onset, including a higher risk of early-onset severe COPD in female smokers [52, 53]. The X chromosome may be involved since COPD in a mother increases the risk of COPD onset in a daughter who smokes [52]. Anatomical factors and the concept of dysanapsis may explain why women are at increased risk of airway diseases [54]. During adolescence, female airway growth is small relative to lung growth to men, whose bronchopulmonary growth is more homogeneous, hence the impaction of inhaled substances on a smaller surface [55]. There is greater particle deposition in healthy women than in men [56] especially in the proximal airways [57]. Another hypothesis is that local inflammatory response in the airways is greater in female than in male smokers. Indeed, respiratory bronchiolitis may occur early in young female smokers [58]. Narrowing of the small airways in women with emphysema is associated with greater bronchial wall thickening [42]. There are also significant differential expressions of certain proteins in alveolar macrophages from male and female smokers with COPD [59]. In women with COPD, impairment in lysosomal function would result in macroautophagy inhibition in alveolar macrophages, thereby contributing to airway inflammation. Leptin, a pro-inflammatory mediator present in the airways of female COPD patients, stimulates the production of certain cytokines; its elevated serum level is thought to be associated with an increased prevalence of COPD in women but not in men [60]. In patients matched for airway obstruction, serum levels of interleukin-16 and vascular endothelial growth factor were significantly higher in female COPD patients than in male COPD patients [61]. Bronchial hyperresponsiveness (BHR) is more common in women than in men, and excessive smoking ( $>20$  g·day<sup>-1</sup>) is associated with a higher risk of significant BHR only in women [62]. BHR is a risk factor for accelerating lung function decline in smokers of both sexes but the rate of FEV<sub>1</sub> decline is more rapid in women [63]. The manner in which smoke is inhaled can change the level of BHR; women tend to inhale more deeply, thus exacerbating BHR [64]. Hormonal factors play a complex role at bronchopulmonary level. The role of oestrogens is well established at several levels: they are involved in maintaining cell structures and in lung elastic recoil that keeps airways open [65]. Accordingly, the level of airway obstruction in post-menopausal women not receiving hormone replacement therapy is greater than in those receiving hormone replacement therapy [66]. The potential anti-oestrogenic effect of cigarette smoke is known [67], and may contribute to impaired lung function in female smokers. After smoke inhalation, chemicals are metabolised in phase I and II, largely mediated by cytochrome P450 (CYP) enzyme inducers. Oestradiol upregulates CYP enzymes of phase I without altering phase II. It increases oxidative stress in the airways making female lungs more susceptible to oxidant damage in response to cigarette smoke [68]. Finally, oestradiol induces MUC5B mucin gene expression in airway epithelial cells in healthy subjects, hypersecretion of the protein being common in chronic respiratory disease [69]. Testosterone aggravates emphysema of the male lung [68]. It increases metalloprotease and elastase effects and alveolar destruction by stimulating neutrophils response.

### Nonsmoking-related COPD

COPD among nonsmokers is an increasing area of study and accounts for 25–45% of patients with COPD [70]. The prevalence of nonsmoking-related COPD is higher among women than among men [24, 71–79]. In the international BOLD study, among 4291 nonsmokers aged  $>40$  years, 6.6% had COPD stage I and 5.6% had COPD stage II or higher [80]. Among smokers, the prevalence of COPD was higher in men (17.1% *versus* 13.2%,  $p=0.001$ ) while among nonsmokers, the age distribution was similar in both sexes (5.2% *versus* 6.2%,  $p=0.142$ ) [80].

Exposure to biomass smoke is thought to be the main risk factor for nonsmoking-related COPD worldwide and occurs mainly in women because they cook in poorly ventilated homes in developing countries [24, 70]. A Chinese study of a large group of nonsmokers found COPD prevalence to be 4% in women and 5.1% in men [81]. The women were slightly younger than the men (51.1 years *versus* 54.4 years) and 92% of them were responsible for cooking compared with 29–52% of the men. Cooking and the use of coal or wood for heating were associated with a higher prevalence of airway obstruction. The risk factors for COPD were living in a rural area, older age, lower level of education, lower income, lower body mass index and a doctor-diagnosed history of tuberculosis.

### Psychological and social impact of COPD: are men and women equal?

Several quality of life questionnaires are available for the study of COPD patients: Short-form (SF) 36, the Medical Research Council Questionnaire and the St George's Respiratory Questionnaire (SGRQ), the last of which is most commonly used. Several studies based on these tools report greater quality of life deterioration in women than in men (table 1) [1, 24, 82, 83]. A French multicentre study [1] compared the SGRQ, the hospital anxiety and depression (HAD) scale and a motivation scale on smoking cessation

TABLE 1 Studies concerned with quality of life by sex in chronic obstructive pulmonary disease (COPD)

First author [ref.]	Country	Quality of life (tools used)	COPD stage	Females/males n	Results
DE TORRES [82]	Spain, single-centre	SGRQ	GOLD II, III	73/73	Quality of life more impaired in females Dyspnoea and arterial saturation: only factors associated with the SGRQ score, unlike males for whom exercise capacity, dyspnoea and comorbidities are found
KATSURA [83]	Japan, single-centre	SGRQ-SF-36, Philadelphia Geriatric Center morale scale	GOLD II	39/117	SGRQ: highest score for activity, impact and total score among females compared with males SF-36 highest score on perceived health and health compared with 1 year ago for females/males
KAPTEIN [84]	Netherlands	Telephone or e-mail questionnaire: intimate physical contact scale (IPCS) or Respiratory Experiences with Sexuality Profiles (RESP)	COPD, asthma	55 patients (of whom 10 females and 15 males with COPD)	Reduced sexual activity in males and deterioration in quality of sex life More seldom occurrence in women
RODRÍGUEZ-GONZÁLEZ MORO [85]	Spain	SF-12 (used during consultations with pulmonologists and treating physician)	GOLD II, III	1786/1661	Quality of life more impaired in females, particularly concerning the mental and physical aspects of SF-12
RAHERISON [1]	France, multicentre	SGRQ, HADS, Q-MAT (for active smokers)	GOLD II, III, IV	247/183	Poorer anxiety and quality of life scores in females even though lung function impairment was less severe than in males

SGRQ: St George's Respiratory Questionnaire; SF: short-form; GOLD: Global Initiative for Chronic Obstructive Pulmonary Disease; HADS: hospital anxiety and depression scale.



in men and in women. The frequency of cough, sputum and severity of dyspnoea did not differ between sexes. The anxiety score was higher and quality of life more impaired in women. In a multivariate analysis, chronic sputum was associated with a poorer quality of life. A Swedish study highlighted the impact of cough and urinary incontinence on quality of life for women and men with COPD [86]. The study placed importance on the reporting of these symptoms during the interview but did not compare the differences between men and women. Female COPD patients with a heavy smoking history seem to experience a poorer quality of life than men with the same smoking intensity [86]. Sex is overlooked in the quality of life scores. A small cohort study looked at a population of patients with COPD and asthma [84]. Patients were asked to answer two questionnaires by phone or e-mail: the Intimate Physical Contact Scale and the Respiratory Experiences with Sexuality Profiles. The female COPD patients described a poorer “quality of sex life” than asthmatic women. However, the scores appeared better than for the men with COPD, particularly in terms of activity and satisfaction. BECKLAKE and KAUFMANN [87] speculated that men attach more importance to athleticism and place less emphasis on dyspnoea as a major symptom. This societal ideal would explain some differences in terms of quality of life and symptom reporting [24]. Conversely, women are less likely than men to report sputum as a symptom. Loss of muscle mass is greater in patients with moderate-to-severe COPD [88] and muscle mass depletion impacts quality of life. This concept is under discussion and some authors suggest a link between muscle mass loss, decreased carbon monoxide diffusion capacity and static hyperinflation [89]. This would tie in with the more common emphysematous phenotype in women. Different methods are used to assess anxiety and depression in COPD patients. In terms of questionnaires, HAD is the preferred method [1, 34, 35, 90–92]; the structured interview approach or medical diagnoses are less common [90, 93].

The incidence of depression is higher in COPD patients than in the general population. Women are significantly more likely to have anxiety and/or depression than men in the COPD population (table 2) with manifestations that can be severe (phobia, panic attacks and generalised anxiety) [90]. The prevalence of depression is significantly higher among women (OR=1.76) [94]. Thus, VANFLETEREN *et al.* [91] have identified a “psychological” phenotype with a female majority of 55%.

The consequences of anxiety and depression are numerous: smoking cessation is more difficult [95]; dyspnoea is increased [94]; quality of life, as measured by the SGRQ or the SF36, is impaired [1, 34, 90, 99, 96]; and sleep disturbances are more frequent [97–99]. The rate of rejection or abandonment of pulmonary rehabilitation is increased [100, 101] and the commitment to self-management of the disease and implementation of action plans to manage exacerbations is lacking [92]. The increased use of care services is linked to an increased risk of exacerbations [35, 102, 103] and increased risk of hospital readmission at 1 year [35]. For MCGARVEY *et al.* [93], female sex and depression are among the risk factors of frequent exacerbations (>2 the previous year). For FAN *et al.* [96], 3-year mortality is significantly increased among patients with depressive symptoms. Anxiety is one of 12 comorbid conditions contributing to excess mortality among the patients concerned, with a hazard ratio of 13.76 [104].

### Lung cancer and COPD in women

Nonsmall cell lung cancer (NSCLC) incidence and mortality have increased in recent years in women [105]. The incidence of NSCLC increased 4–5 times faster than the general population in patients with COPD over the period 1991–2001 in the UK, regardless of sex [106]. COPD itself is an independent risk factor for NSCLC above and beyond its association with smoking [107]. The impact of COPD on mortality is negligible in some studies [108, 109], whereas according to the study by KIRI *et al.* [106], COPD increases 3-year mortality in patients with NSCLC regardless of patient age or sex, with higher mortality rates above all in patients aged >65 years (RR=2.05 against 1.3 in patients aged <65 years). Few studies focus on women with COPD and presenting with NSCLC. In the study by IZQUIERDO *et al.* [109], 47.7% of patients with stages IIIB and IV NSCLC also had COPD, while in the study by LOGANATHAN *et al.* [105], 72.8% of men with NSCLC and 52.5% of women with NSCLC also had COPD, regardless of the TNM (classification of malignant tumours) stage of the disease. In a study of 562 North American women aged

TABLE 2 Prevalence of anxiety and depression in patients with chronic obstructive pulmonary disease (COPD) according to sex

First author [ref.]	Population	Patients n	COPD	Females %	Anxiety	Depression	Anxiety and depression
DI MARCO [34]	Italian	202	Moderate to severe	23.3	38.3/25.2	38.3/12.9	25.5/6.5
LAURIN [90]	Canadian	116	Moderate to severe	53	56/35	24/12	Not provided
RAHERISON [1]	French	430	Moderate to severe	57.4	29.4/16.8	19/4.6	Not provided

Data are presented as females/males %, unless otherwise stated.

18–74 years who were diagnosed with NSCLC, an increased risk of developing NSCLC before 55 years of age was seen in women with COPD (OR=1.67) compared to women without COPD. This effect was not present in the subgroup of African-American women. Emphysema was associated with an increased risk of NSCLC in women with COPD (OR=3.21). A history of chronic bronchitis also increased the risk of NSCLC (OR=1.7) [110]. The median time between COPD diagnosis and NSCLC diagnosis was 13 years regardless of age at diagnosis of NSCLC, but the average age of onset of COPD was 35 years for patients diagnosed with NSCLC before 55 years of age, compared to 51 years if the diagnosis of NSCLC was made after 55 years of age. The authors suggest a possible genetic susceptibility to early onset of lung disease and then NSCLC [110] in female smokers. In support of these findings, several pathophysiological hypotheses exist in the literature. DNA repair capacity is thought to be 10–15% lower in women than in men [111]. Women are said to have higher levels of DNA adducts and more DNA damage [111]. Increased metabolic bioactivation relating to tobacco use (hydrocarbons) was also a proposed hypothesis [111]. Women are thought to have increased expression of CYP (cytochrome P450 gene) enzymes in the distal airways that would be upregulated by oestrogen receptor- $\alpha$  [111]. Finally, oestrogens might influence NSCLC onset regardless of sex [112, 113] by oestrogen receptor- $\alpha$  and - $\beta$  expression in lung adenocarcinoma cells [112].

### Therapeutic care

Analysis of the effects of smoking cessation according to sex has been the subject of several studies involving very large samples. The “Lung Health Study” [49], which set out to assess lung function parameters in patients with mild-to-moderate COPD, found that FEV<sub>1</sub> gain was greater in women than in men at 1 year (3.7% versus 1.6%;  $p < 0.001$ ) if smoking cessation was successful, and at 5 years, although the difference between the two sexes was less marked. Furthermore, the relationship between FEV<sub>1</sub> slope of decline and bronchial hyperreactivity was more significantly correlated in women than in men ( $p < 0.001$ ). These findings confirmed those obtained in two previous Danish [114] and Canadian [50] cohorts, which showed that the greater the women’s past smoking habit, the greater the beneficial effects of smoking cessation [114]. Moreover, the female population appears to be more sensitive to the harmful effects of smoking [115]. However, it would appear that women find it harder than men to stop smoking and are more likely to relapse because of less clinical improvement after smoking cessation and potential weight gain [29, 49]. These factors justify the use of highly tailored cessation strategies designed specifically for women. A background of anxiety and depression complicates smoking cessation. Studies that have investigated the effect of pharmacological smoking cessation aids including bupropion and varenicline seem to find them equally effective in men and women [29, 116], although the efficacy of nicotine transdermal patches is more pronounced in the male population [117]. Women have stronger immune responses than men after a flu vaccination. They have more frequent adverse reactions than men, but the vaccination is more effective [118]. Given the small number of studies devoted to the influence of sex on the medical treatment of COPD, the published results might appear conflicting. Thus, an old study [119] on a small population suggested that, irrespective of age, the inhalation technique proved less effective in women than in men, with 4% of the female population satisfied with its use compared with 43% of males. This finding was not confirmed in a more recent study, which however did not control the extent to which patients were educated on the use of inhalers [120]. Similarly, the findings diverge in terms of compliance; women with mild-to-moderate COPD were reportedly more treatment compliant, whereas compliance was reported to be more satisfactory in men with severe COPD [121]. Few studies focus on the efficacy and tolerability of these treatments by sex. The study by VESTBO *et al.* [122] on salmeterol/fluticasone coadministration found no difference in therapeutic response between men and women in terms of FEV<sub>1</sub>, frequency of exacerbations and quality of life. Another study of tiotropium showed identical effects on lung function, respiratory symptoms and quality of life in the female and male population [123]. A similar finding could be extrapolated from the results published in the TORCH study, in which treatment response was unaffected by sex, although the study was not designed to answer this question [124]. The lower proportion of women in the majority of studies makes it difficult to evaluate the pharmacology and effects of the different therapeutic classes used in COPD. We have little data on the differences in sex-based physiology and respiratory anatomy to make a potential effect on dose delivery and on the efficacy of inhaled therapies. However, the likelihood of a deterioration in clinical respiratory status (symptoms and exacerbations) on discontinuation of inhaled corticosteroids seems greater in female than male patients with COPD [125]. Finally, special attention should be paid to inhaled corticosteroid use in women given the increased risk of osteoporosis, justifying supplementation with vitamin D, calcium and bisphosphonates.

Osteoporosis is characterised by compromised bone strength and microarchitectural deterioration of bone tissue, leading to bone fragility and increased fracture risk. Its prevalence in COPD ranges from 24% to 69% [126]. The risk factors for COPD, smoking and menopause, are compounded in women with COPD. Oral corticosteroids are a recognised risk factor at a cumulative prednisone equivalent dose  $>7.5$  mg daily for more than three consecutive months. The effects of long-term use of high-dose inhaled corticosteroids



TABLE 3 Osteoporosis risk factors

Major factors	Minor factors
Systemic corticosteroids for >3 months-year <sup>-1</sup>	Body mass index <21
Prior vertebral compression fracture	Active smoker
	Chronic alcoholism
	Aged >65 years
	Hip fracture
	Rib fracture
	Menopause
	Sedentariness
	FEV <sub>1</sub> <50% of theoretical value

FEV<sub>1</sub>: forced expiratory volume in 1 s.

have been reported previously [127, 128]. In post-menopausal women, the risk factors identified in addition to fracture risk were: body mass index <19, onset of menopause before the age of 40 years, and history of femoral neck fracture in a first-degree relative [129]. Pulmonary rehabilitation, which includes smoking cessation and exercise training, plays a key role in the treatment and prevention of osteoporosis; its beneficial effects on bone mineral density, strength muscle, balance and fall risk have been proven [107]. Calcium and vitamin D supplementation are effective in reducing fracture risk with a vitamin D dose-dependent effect only when combined with calcium [130]. A daily dose of 800 IU of vitamin D and 1 g of calcium is recommended with a T-score more than -1 with three minor risk criteria or one major risk criterion (table 3) [131, 132]. The value of antiresorptive therapy with bisphosphonates has been demonstrated in post-menopausal women in the steroid-induced forms of osteoporosis and in obstructive respiratory disease [133, 134]. Teriparatide appears beneficial in the treatment of glucocorticoid-induced osteoporosis but its value in COPD patients has yet to be established [133]. There are as yet no specific recommendations for COPD patients, let alone women with COPD [129, 135–137].

The majority of studies investigating the effects of oxygen therapy specifically for the treatment of COPD in men and women seem to have found a benefit in women. The study by MIYAMOTO *et al.* [138] in 1995 found that women on long-term oxygen therapy experienced significantly better survival, with a persistent difference after controlling for age, blood gas analysis and lung function. These results were confirmed by a Swedish cohort study of 5689 patients on oxygen therapy and followed up for >10 years, with a relative risk of excess mortality among men of 1.21 [139]. In other words, first year survival was 77% in women and 69% in men. More recent still, another cohort study in a larger population, whose mortality was assessed according to their comorbid conditions, confirmed the mortality reduction among women [32]. This latest study made it possible to establish that, although the significance of the comorbidities found in these patients is an independent predictor of mortality, female mortality was lower, even after adjusting for these comorbidities.

The explanation for this difference is not fully clear given that there was no difference in FEV<sub>1</sub> between the two sexes at the start of oxygen therapy. Treatment initiation does not appear earlier in women, especially since their arterial oxygen tension was lower than that of men when therapy was indicated. It is difficult to ascertain whether compliance with oxygen therapy differed given that it was rarely controlled. It is possible that the smoking cessation usually achieved through the introduction of oxygen therapy has been more beneficial for women, as described earlier in this chapter. Differences in environmental and occupational exposure, together with phenotypic differences accounting for the greater frequency of emphysema in men, could be implicated.

The improvement in exercise capacity and quality of life after pulmonary rehabilitation appears identical in men and women [140]. These programmes appear to be beneficial for women as they take into account many factors, including the role played by therapeutic education and its additional positive impact on anxiety and depression. However, Foy *et al.* [141] found that, despite a similar improvement in both sexes in terms of symptoms and quality of life after 3 months of exercise training, these benefits persisted only in men at the 18-month assessment. These results should be interpreted with caution in the absence of data on the exercises performed to maintain the gains achieved. Moreover, the expected benefits of pulmonary rehabilitation might differ between the sexes.

## Conclusion

COPD in women is a major public health issue. It is biologically plausible that women are more vulnerable to nicotine addiction or environmental factors than men. More evidence is required, particularly to elucidate the role played by hormones.

In developing countries, COPD affects women differently to men, not only because of nicotine addiction, but also because of environmental exposure to biomass fuels.

The risk of death associated with active smoking among women increases with the number of cigarettes smoked and the age at which they become active smokers.

The perception of COPD has changed. It increasingly affects women, who differ in terms of both clinical presentation of symptoms and exacerbations and radiological presentation. Primary care professionals and pulmonologists must rise to the challenge of improving treatment through early diagnosis and shared knowledge of the specific features of COPD in women in primary care medicine.

To conclude, women remain under-represented in controlled clinical trials and few studies have investigated therapeutic response to COPD treatment according to sex.

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