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CLINICAL REVIEW

Reconsidering sex-based stereotypes of COPD

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Abstract

Chronic obstructive pulmonary disease (COPD) has historically been considered a disease of older, white, male smokers, as illustrated in Frank Netter's classic images of the 'pink puffer' and 'blue bloater'. However, women may be more susceptible to COPD than men, and the disease course may be reflective of that increased susceptibility. From a review of epidemiological data of COPD, we found differences in the way men and women present with COPD symptoms, a bias in the way COPD symptoms are treated in men and women, and differences in susceptibility to airway obstruction based on age, sex, and smoking history. These data show that classic stereotypes of COPD – including male predominance – should be abandoned, and that there are not two but multiple COPD phenotypes, which are characterised by differences between women and men in susceptibility, symptoms, and disease progression. These differences impact on physician perception. Although further research into this concept is needed, the differences we found should prompt, in the short term, changes in the way (and in whom) COPD is evaluated, diagnosed, and treated; in the long term, these differences should prompt research into the prognosis of COPD based on sex differences.

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Introduction

Chronic obstructive pulmonary disease (COPD) is the fastest growing and fourth leading cause of death in the USA.[1] Men and women present with COPD symptoms in very different ways. There is a bias against the diagnosis of COPD in women versus men, and there is growing evidence for differences in susceptibility to airway obstruction between men and women. We provide evidence that COPD may present as multiple phenotypes in both men and women, which extend beyond the scope of the classic Netter illustrations of the 'pink puffer' and 'blue bloater'. Awareness of this changing paradigm of COPD is important because COPD is most commonly diagnosed and managed by family physicians and generalists. The purpose of this review is to highlight new data that show that there are not two but multiple COPD phenotypes, characterised by differences between women and men in susceptibility, symptoms, and disease progression, and that these differences impact on physician perception.

Methods

A literature search was performed on PubMed, EMBASE, and Web of Science using the terms 'sex AND COPD', 'gender AND COPD', and 'female AND COPD', followed by a review of related articles based on references from the initial search. The review was limited to the English language literature.

COPD redefined

Only a minority of smokers (15–44%) develop COPD,[2,3] and individuals with COPD more frequently have cigarette-related co-morbidities than controls without COPD matched for age, sex, and smoking status.[4] These co-morbidities – which reflect the systemic nature of COPD – include cardiovascular disease,

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peripheral vascular disease, systemic hypertension, and lung cancer.[5-9] Even non-cigarette-related conditions such as osteoporosis, depression, muscle wasting, cachexia, and the metabolic syndrome are more common in individuals with COPD than similarly matched smoking controls.[10-14] The pattern of which and how many of these co-morbidities are present in an individual and the physiological and anatomical manifestations of these diseases all help to make up the 'phenotype', which is defined as the observable characteristics of an individual as determined both genetically and environmentally. The Netter illustrations of the 'pink puffer' and 'blue bloater' highlight emphysematous and bronchitic phenotypes of COPD – in older men. These should be viewed as anatomical and physiological elements of the various COPD phenotypes that have very different prevalences in men and women (see discussion of computed tomography patterns below). Other emerging COPD phenotypes highlight the systemic nature of this disease, which also affects men and women differently.

Susceptibility

Susceptibility is the capability of submitting to or inability to resist an action, process, operation, or risk factor. All of the following are considered to be risk factors for COPD: genes, inhalational exposure, lung growth and development, oxidative stress, infections, socioeconomic status, nutrition, and asthma.[15] Sex is also a risk factor for COPD because there is an interaction between sex and many of the above-stated risk factors.[15] First, sex affects genetic susceptibility. Silverman and colleagues found a markedly elevated prevalence of women (71.4%) in a study of 84 probands with severe early-onset COPD. Furthermore, smoking female first-degree relatives of early-onset COPD probands were almost twice as likely to experience airway obstruction and 3.5 times more likely to have severe obstruction (forced expiratory volume in one second (FEV_1) <40%) than male relatives who smoked.[16] Sex also affects the type of COPD-provoking exposure. Women experience less first-hand but more second-hand tobacco smoke exposure than men.[17] In developing countries where biomass fuels are used to heat homes and cook meals, women develop COPD more frequently from indoor air pollution than from cigarette exposure.[15,18-21] Exposure to biomass fuels, occupational exposures, and remodelled asthma are important causal agents in the estimated 15% of individuals with COPD who have never smoked.[22,23]

Differences in lung growth rates between males and females combined with early age of smoking initiation[24,25] and sex-specific smoking behaviours[26,27] further enhance the susceptibility of women to tobacco smoke. Girls have an earlier and more accelerated lung growth than boys but, at adulthood, women have smaller lungs than men.[28] Age-related loss of elastic recoil occurs later in women.[28] In a UK study, smoking initiation at an early age (<16 years) was associated with a lower FEV_1 in both male and female current smokers and ex-smokers; however, this effect was most apparent in female current smokers.[24] Similarly, Gold and co-workers showed that early exposure to as few as five cigarettes/day resulted in a fivefold greater reduction in lung growth rate in girls than in boys.[29] Women have a lower socioeconomic status than men in many countries, which can affect nutrition and frequency of respiratory tract infections.[30] Sex hormones have also been shown to modulate oxidative stress and aging[31,32] and alveolar regeneration.[33]

Epidemiological data regarding enhanced susceptibility of women over men to COPD is mixed, but generally compelling. Methodological differences in studies that may be responsible for these inconsistencies include:

(1) Failure to compensate for cigarette consumption. Women tend to smoke fewer cigarettes and to have different smoking patterns from men. Women more commonly smoke both filtered and mentholated cigarettes.[34] They generally smoke fewer cigarettes per day, and urinary cotinine levels (corrected for the number of cigarettes smoked) are lower in women.[34] However, Leynaert and co-workers have suggested that the smaller airways in women may expose their lungs to a greater dose of smoke/cigarette than men.[35]

(2) Exclusion of subjects who display bronchial hyperreactivity (BHR). Women with COPD are more likely to have BHR than men.[35-38] BHR is a predictor of COPD severity because it is indicative of both the rate of progression of COPD and death due to the disease.[36,39,40]

(3) Measurement of susceptibility by annual decline of FEV_1 in mL rather than in percent predicted FEV_1 or lower limit of normal. Because women have, in general, smaller body size than men, their annual decline in FEV_1, as measured in mL, would underestimate their true loss of lung function.

Evidence for enhanced susceptibility of women for COPD includes studies that show an increased rate of decline in FEV_1 in women compared with men[25,41-46] and an increased rate of COPD-related events.[1] A recent systematic review and meta-analysis of 11 population-based cohort studies showed that the annual decline in percentage predicted FEV_1 was greater for women than for men.[46] A case-control study of patients with stable COPD attending a pulmonary clinic in Spain showed that women, when matched with men for percent predicted FEV_1, were younger (48±28 vs. 65±8 years, p=0.001), smoked less (48±28 vs. 69±27 pack-years, p=0.001), had more exacerbations in the previous year (1 vs. 0, p=0.009), and performed worse on the 6-minute walking distance test (87±18 vs. 105±22 percentage predicted, p=0.001; 444±85 vs. 518±92 metres, p=0.001) than men.[47] In another study, women started smoking at an older age (17 vs. 15 years, p<0.001) and had fewer pack-years of smoking (20.5 vs. 38.3, p<0.001) than men with comparable percent predicted FEV_1 (81.5% females vs. 79.2%

males, p=0.279).[45] Finally, a long-term study of smokers in the Netherlands suggested that FEV_1 declined more rapidly in women smokers than in men who smoked.[42-44]

The cause of increased susceptibility in women is unknown. The most obvious factor would be oestrogen-related, and several studies have shown that post-menopausal women who use hormone replacement therapy (HRT) experience less pulmonary function decline and less inflammation than older women who do not take exogenous hormones.[31,48-50] In the Cardiovascular Health Study, spirometry was performed on 2,353 women older than 65 years who could provide information on HRT use. FEV_1 was higher overall in women who were currently using HRT than in those who were not currently using HRT (1.82 L vs. 1.66 L, p<0.0001), including former smokers (currently using versus not currently using HRT: 1.76 L vs. 1.60 L, p=0.013) and never smokers (1.90 L vs. 1.72 L, p<0.0001). Overall, HRT users were also 25% less likely to have airways obstruction than women not currently using HRT.[31] Similar findings were also seen in a small study (N=85) in which women who used HRT were 88% less likely to have BHR than non-HRT users, although mild BHR showed no association with HRT use.[49] However, the relationship of sex hormones to COPD is probably complex, given that women appear as a group to be more susceptible to COPD than men. Clearly, more research is needed on the link between oestrogen and susceptibility.

Increased susceptibility should translate into increased prevalence. However, few studies show a greater prevalence of COPD in women than in men. This is probably related to the presence of the same methodological biases that plague susceptibility studies, and the fact that insufficient time had elapsed to show the effects of enhanced susceptibility on prevalence. For example, in the National Population Health Study of Canada, the prevalence of COPD was higher in women overall (8.2% vs. 3.5%) and in female non-smokers (2.1% vs. 0.8%), but equivalent between the sexes in smokers (2.7% women vs. 2.8% men).[51] In current smokers the prevalence of COPD was 10.1% in women compared with 3.8% in men who started smoking before age 18. The age at which women started smoking had a dramatic effect on the prevalence of COPD compared with men. For those who started smoking after age 18 (and were current smokers), COPD prevalence was still twice as high in women as in men (5.9% vs. 3.0%). In ex-smokers there was no difference in the prevalence of COPD between the sexes.[51] In contrast, De Torres and co-workers found that the prevalence of COPD was higher in men than in women (30.5% vs. 22.3%, p<0.001) with similar degrees of obstruction (FEV_1 78% of predicted in men and 75% of predicted in women) and irrespective of the pack-year smoking history. However, in this study, persons with a positive bronchodilator response were excluded.[52] A 25-year follow-up study of the general population in Copenhagen showed no difference in COPD prevalence between men and women; however, the authors noted that classification of smoking history was not detailed. Because men smoked more tobacco daily than women at that time in Denmark, a higher susceptibility of women to COPD per gram of tobacco may have been masked. The higher risk for women in this study was only discovered when tobacco consumption was measured in detail.[53] An Austrian study showed that COPD was as common in women as in men but, when compared across age groups, it was more common in women in the 40–49-year age group.[54] In studies using self-report for calculation of prevalence values the results are also mixed. The National Health Interview Study found a greater number of women than men (7.2 vs. 4.4 cases/million) with chronic bronchitis and emphysema. By contrast, in the National Health and Nutritional Examination Study (NHANES) there were 74.3 vs. 58.2 self-reported cases of COPD per 1,000 men and women, respectively. A recent meta-analysis of 62 population-based studies from 1990 to 2004 showed a prevalence of 2:1 in men versus women for COPD.[55]

Symptoms

Women present with COPD differently from men. Female COPD patients report a higher level of dyspnoea for the same level of ventilatory impairment than men.[56,57] In the Confronting COPD International Survey, women were more likely to report severe dyspnoea than men (odds ratio (OR) 1.30, 1.10–1.54), with similar cough (OR 1.08, 0.92–1.27) and less sputum (OR 0.84, 0.72–0.98), despite significantly lower pack-years of smoking (mean (SD) 36 (29) vs. 46 (35) pack-years).[58] Women enrolled in the National Emphysema Treatment Trial (NETT) also experienced greater dyspnoea and lower quality of life than men matched for precent predicted FEV_1, age, proportion of the lung affected by emphysema, and pack-years.[59] Two studies by De Torres and co-workers have similarly shown differences between men and women with regard to reporting of sputum and dyspnoea.[47,52] Women with COPD tend to report more cough than men but less sputum; however, this may be a cultural/societal artefact as women tend to swallow phlegm and may be less likely to admit to having it.[45] Regardless of whether the increased reporting of dyspnoea with reduced reporting of sputum among women compared with men is related to patient perception or reality, knowledge of this difference is important when formulating a differential diagnosis. Contrary to the above, Watson and colleagues found similar reporting of symptoms between the sexes in the 816 men and 312 women enrolled in the EUROSCOP Study.[60] In this study, as with the other reports noted above, men but not women reported an improvement in symptoms with treatment-induced improvement in FEV_1.

Overall, women with COPD have a lower health-related

quality of life (HRQL) corrected for FEV_1. In a recent study evaluating HRQL in outpatients with COPD (1,786 women and 1,661 men), women showed significantly lower scores in all physical and mental domains of the HRQoL measures (SF-12) than men. The physical component of the SF-12 was especially impaired in women compared with men of the same age and severity of COPD.[61]

Co-morbidities

Women tend to experience more co-morbidities and of a different pattern than men. Depression and anxiety are common COPD co-morbidities that affect the hospitalisation rate and quality of life.[56,62] Women with COPD suffer more from depression and have a lower quality of life than men.[47,56,59,63-67] Women also appear to employ different coping strategies for COPD than men.[68]

Airflow obstruction is associated with a 4–5-fold increase in lung cancer when all other risk factors are controlled.[5-7,69] Although lung cancer is more common in smokers with airflow obstruction than those without, women may be more susceptible to smoking-related lung cancer than men.[70-73]

Osteoporosis, which is typically thought of as a disease of Caucasian women, has a higher prevalence among smokers with airflow obstruction regardless of sex. Sin and co-workers have shown that the severity of osteoporosis can be linked to the severity of COPD measured by FEV_1.[11] This association between COPD severity and osteoporosis severity is probably related to bone mineral metabolism abnormalities found in smokers,[74] premature menopause in women smokers, use of systemic steroids for COPD exacerbations, and inactivity related to COPD-associated exercise limitation.

Diagnosis

Diagnostic testing

Data from the NETT, the National Lung Screening Trial, and the GlaxoSmith Kline International COPD Genetics Network all show that women have less emphysema than men; however, based on computed tomography scanning, airway thickness appears to be increased in women.[32,59,75] While other studies have confirmed these findings, recent data suggest that the progression of emphysema with age is increased in women compared with men.[76] Another recent study showed that airway thickness and the percentage of emphysema are dependent upon age and smoking status.[77] In contrast to other studies noted above, this study shows that there are more cases of emphysema in men than in women, and airway thickness was increased in men compared with women.

Also in the NETT, women had lower carbon monoxide diffusion capacity and oxygen pressure, higher carbon dioxide pressure, shorter 6-minute walk distance, and lower maximal wattage during oxygen-supplemented cycle ergometry than men despite less severe airways obstruction.[59] Women also experienced a higher BODE index (body mass index/airflow obstruction measured by FEV_1/dyspnoea measured on a modified British Medical Research scale/exercise capacity measured by 6-minute walk test) for a given percent predicted FEV_1, age, number of pack-years, and proportion of emphysema than men.[59] Other studies have confirmed these physiological differences between women and men with COPD.[47,52,76]

Diagnostic bias

COPD may be diagnosed less frequently in women than in men perhaps because of a bias against recognising COPD symptoms (and therefore pursuing a diagnosis) in women compared with men. COPD is currently defined as an FEV_1/forced vital capacity (FVC) < 70% and is diagnosed based on both clinical history of COPD symptoms (cough, wheeze, sputum, and dyspnoea upon exertion) with confirmation of obstruction on spirometry.[15] As noted, the pattern of symptoms reported by women is different than for men, which may result in less spirometric testing in women than in men. Watson and co-workers showed that women who presented with signs or symptoms of COPD were less likely to have spirometric testing than men (OR 0.84, 95% CI 0.72 to 0.98) but, ironically, were more likely to get smoking cessation advice than men (OR 1.57, 95% CI 1.33 to 1.86).[58] Further illustrative of the bias in diagnosing COPD in women is a study of Canadian and American primary care physicians using a hypothetical case presentation of cough and dyspnoea in a smoker, presented in six versions differing only in the age and sex of the patient. After presentation of the history and physical findings, the physicians were asked to state the most probable diagnosis and to choose the diagnostic studies needed. The physicians were then presented with spirometric findings of moderate or severe obstruction without significant bronchodilator response and again asked for a provisional diagnosis. They were finally told of a negative outcome of an oral steroid trial. Initially, COPD was given as the most probable diagnosis significantly more often for the male than for the female case presentations. In this study the physicians more often diagnosed the women (incorrectly) as having asthma. These initial significant sex-based differences decreased as objective information from spirometry was provided. Unfortunately, only 21.8% of the study physicians would have requested spirometry after the initial presentation.[78] In a similar study in Spain, COPD was more likely to be the preliminary diagnosis for male patients than for female patients (OR 1.55, 95% CI 1.15 to 2.1), but the sex bias disappeared once the physicians were shown spirometry results.[79] This apparent bias may be fading, however, as a more recent study involving five US health plans that covered 1.6 million members showed that women smokers were slightly more likely than men to undergo spirometry (33% vs. 29.4%,

p=0.001).[80] However, a diagnostic bias still remains in self-report as illustrated by an emergency department study that found women more commonly reported a mixed diagnosis of asthma and COPD than men (48% vs. 39%) when presenting with an exacerbation of obstructive lung disease.[81]

Treatment

Smoking cessation

Women are generally less successful at long-term smoking abstinence than men.[38,82,83] Women tend to anticipate more barriers to smoking cessation,[84] to experience greater depression with a smoking cessation attempt,[84] and have higher behavioural but lower nicotine dependence.[83] These tendencies may explain why women appear to benefit from exercise as an aid to smoking cessation and men do not.[85] While both bupropion[86] and varenicline[87,88] have equal efficacy in women and men, women are less successful at achieving sustained smoking abstinence with nicotine replacement therapy than men.[89,90] The difference in efficacy of nicotine replacement therapy between men and women may be related to the relatively flat nicotine response curve of women compared with men,[89] or may be due to women's accelerated rate of metabolism of nicotine compared with men.[91]

Bronchodilating agents

Bronchodilators are the mainstay of pharmacotherapy for COPD.[15,92] Long-acting bronchodilating agents are recommended as maintenance therapy for GOLD stage 2 and above (post-bronchodilator FEV_1 <80% predicted) and short-acting bronchodilating agents are used on an as-needed basis at every GOLD stage. While response to the short-acting β_2-agonist albuterol is significantly greater in men than in women when measured in mL, when measured in percent predicted FEV_1 this difference is lost.[93] Similarly, the bronchodilating response to the short-acting anticholinergic ipratropium bromide and long-acting bronchodilators tiotropium and salmeterol is equivalent in men and women (data on file, Boehringer-Ingelheim). More recent analysis of the dataset from the UPLIFT trial (a study evaluating the effects of tiotropium on rate of decline in FEV_1 in 5,992 patients, 75% men, 25% women) showed that women with COPD were younger than the men and were more commonly current smokers but had fewer pack-years. Rates of decline in both pre- and post-bronchodilator FEV_1 and FVC were slightly lower for women than for men in absolute terms, but similar when expressed as the yearly decline in percent predicted (co-primary endpoints). Similarly, hazard ratios (HR) for first exacerbation (tiotropium/placebo) were similar in men and women (0.87, 95% CI 0.81 to 0.93 for men and 0.83, 95% CI 0.74 to 0.94 for women). Exacerbations requiring hospitalisations (a secondary endpoint) declined in both, but to a greater extent in women (HR 0.77, 95% CI 0.62 to 0.94) than men (HR 0.89, 95% CI 0.79 to 0.99). Women had worse baseline HRQoL as measured by the St George's Respiratory Questionnaire, but both men and women improved to the same extent. Improvement in survival was similar.[94]

For GOLD stage ≥3, combination therapy including an inhaled corticosteroid is recommended. Bronchodilator effect and the effect on disease modification endpoints such as exacerbation frequency, rate of decline in FEV_1, and mortality for an inhaled corticosteroid coupled with the long-acting bronchodilators salmeterol or formoterol are also equivalent in men and women.[95-100]

Pulmonary rehabilitation

Women tend to complain of more dyspnoea than men for a given decrement in FEV_1. Despite this seeming impediment to physical rehabilitation, sex does not influence pulmonary rehabilitation outcomes even in severely dyspnoeic subjects.[101,102] However, when short (3 months) versus long (18 months) duration pulmonary rehabilitation was compared in men and women, only men experienced continued benefit in HRQL after 3 months of therapy.[103]

Supplemental oxygen

While women appear to be more susceptible to hypoxaemia than men, hypoxaemia has a less detrimental effect on survival in women than in men. A study of Swedish COPD patients receiving oxygen therapy showed that the annual incidence and prevalence of starting oxygen therapy increased more rapidly in women than in men, yet survival was better in women with long-term oxygen therapy than in men: median (first and third quartile) survival was 2.8 (2.6-2.9) years in women vs. 2.0 (1.9 to 2.1) years in men with a relative risk for death of 1.21 (95% CI 1.14 to 1.28).[104] In another study the HR for death in men versus women on supplemental oxygen was 1.54 (95% CI 1.15 to 2.07).[105]

Prognosis

Data from the National Vital Statistics analysed by the Centers for Disease Control and Prevention show that, during the years 2000–2005, the annual death rate from COPD increased by 5% annually for men and 11% for women, further widening the gap in mortality between women and men.[106] Hospitalisation for COPD increased in women by 43% and in men by 12% over the interval 1980–2000. Women with COPD are more likely to be hospitalised for COPD and to die from it than men, even when adjusting for smoking history.[44,107] In one study the increased relative risk for women ranged from 1.5 (95% CI 1.2 to 2.1) to 3.6 (95% CI 1.4 to 9.0).[44] However, in another study, when men and women were matched by BODE index, survival was significantly better for women.[108] Women also appear to be at increased risk of death from COPD-related co-morbidities.[109] Swedish census data show that female smokers display slightly higher relative death rates from

ischaemic heart disease when the effect of the amount of cigarette consumption is considered.[110]

Conclusions

Although this study is not a formal meta-analysis, this review of epidemiological and clinical data indicates that the paradigm of COPD is changing from a male-predominant two-category disease to a disorder characterised by multiple co-morbidities with a growing female prevalence. Dyspnoea on exertion, wheeze, and cough with sputum are the cardinal symptoms of COPD. Yet women seem to over-report dyspnoea and under-report sputum production compared with men. Doctors tend to underutilise spirometry relative to the frequency of patient reports of symptoms. Therefore, an important first step towards addressing any sex differences in COPD and for better overall management of COPD is for physicians actively to solicit the report of respiratory complaints in smokers and to perform spirometry when symptoms are present. Although further research into this concept is needed, physicians also need to realise that women's complaints related to COPD are different from men's, and the disease course in women is different (increased susceptibility, faster rate of FEV_1 decline, more hospitalisations, more dyspnoea, more deaths from COPD).

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Conflicts of interest

Dr Ohar is not a consultant nor does she have research contracts. Dr Fromer, Speakers Bureau for BI and Pfizer. Dr Donohue is a consultant for BI. He receives honoraria for lectures and has reseach contracts between BI and UNC that he is the principal investigator.

Contributorship

Dr Ohar performed the research and literature search, wrote the first draft, and led the manuscript review process. Dr Fromer served as a co-author and provided original content as well as editorial review of the content of this paper. Dr Donohue participated in the writing, research and literature search as well as the manuscript review process.

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COMMENTARY

Sex and gender differences in COPD: challenging the stereotypes

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The relationship of sex and gender to health and disease is complex, and varies across an individual's lifespan. This has implications for (potentially) differing patterns of disease prevalence, different degrees of severity, and different patterns of mortality and morbidity between men and women.[1,2]

Sex denotes the differences attributed to biological origins alone, while gender refers to the social and cultural influences that lead to differences between women and men.[3]

Chronic obstructive pulmonary disease (COPD) is an increasing cause of morbidity and mortality worldwide. Although COPD has historically been considered a disease of male smokers, it now clearly impacts on both sexes.[4] As Ohar, Fromer, & Donohue point out in this helpful review,[5] the paradigm of COPD is changing from a male-predominant two-category disorder, to a disorder characterised by multiple co-morbidities with a growing female prevalence.

Careful evaluation, and a raised awareness of the possibility that sex or gender (or both) may influence COPD susceptibility and progression, is of critical importance for two main reasons: firstly, because the potential future impact of the disease may have been underestimated;[4] and secondly, because the condition is primarily diagnosed and managed by general practitioners (GPs). GPs are as vulnerable as their patients to sex and gender stereotypes, and this can impact on information processing and decision-making.

This review[5] highlights key research areas in COPD where sex and gender stereotypes can be challenged – including disease susceptibility, symptoms, treatment, prognosis, and diagnosis. Although biological determinants of sex and age differences in airway behaviour (dimensional, immunological, and hormonal) have been known for many years,[6] there are still major gaps in our knowledge about COPD phenotypes. In particular, little is known about the mechanisms and

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