Review Article

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Chronic obstructive pulmonary disease: A review about gender differences

Carolina Santos[1], Tiago Pereira[1], Raquel Barros[1,2]

ORCID:
Carolina Santos: 0000-0002-6692-9504
Tiago Pereira: 0000-0003-3715-652X
Raquel Barros: 0000-0003-1712-028X

Abstract:

The major risk factor for chronic obstructive pulmonary disease (COPD) is smoking. COPD is thought to be traditionally a male illness, but its prevalence in women is increasing because they are adopting lifestyle habits similar to men. A literature review of publications indexed in MEDLINE, Latindex, SciELO, and DOAJ databases was carried out. Were considered 44 articles with relevance to the topic addressed. The literature review aim was to characterize the gender susceptibility differences in COPD development as well as the changes that this disease may induce in the lung function. Through the present literature review, it was verified that there are multiple aspects that contribute to gender inequalities in COPD development. Among them are genetic predisposition, hormonal factors, tobacco smoke components metabolization, anatomical and physiological characteristics, bronchial hyperreactivity, and noxious agent's exposure. Gender differences in deleterious effects of tobacco smoke on lung function do not hold consensus, as there are authors reporting a greater lung functional decline in women even when less exposed to harmful substances, while others have found no differences in many of lung functional parameters. The studies analyzed were different regarding methodology and sample characteristics, which may contribute to results discrepancy obtained by the researchers. COPD affects men and women in increasingly similar proportions, so it is important to identify and characterize the particularities of tobacco smoke effects in both genders to improve the knowledge about the disease.

Keywords:

Chronic obstructive, gender identity, pulmonary disease, respiratory function tests, smoking

[1]Department of Cardiopulmonology, Portuguese Red Cross Health School, [2]Department of Pulmonology, University Hospital North Center Lisbon - Pulido Valente Hospital, Lisbon, Portugal

Address for correspondence:
Dr. Raquel Barros, Centro Hospitalar Universitário Lisboa Norte, Hospital Pulido Valente Edifício Rainha Dona Amélia Piso 2, Unidade de Fisiopatologia Respiratória Alameda Das Linhas Torres 117, 1769-001 Lisboa, Portugal.
E-mail: rbarros@esscvp.eu

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Introduction

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD)-2019,[1] chronic obstructive pulmonary disease (COPD) is defined as a common, preventable, and treatable disease is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.

Spirometry is essential for diagnosis, characterization, and follow-up of COPD. According to the GOLD, the existence of forced expiratory volume in the first, second, and forced vital capacity ratio (FEV_1/FVC) <0.70 postbronchodilator confirms the presence of persistent airflow limitation, and the FEV_1 parameter classifies obstruction severity. Lung function in COPD patients declines over time; therefore, monitoring airflow limitation should be a part of regular evaluation,[1] recommended at least once a year. GOLD 2017 has removed spirometry from combined COPD assessment being used only in diagnosis and airflow limitation severity assess. A weak correlation between FEV_1 symptoms, and impairment of

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the patient's health status has been stated. In individuals with COPD, the performance of other lung functional techniques (e.g., whole-body plethysmography, diffusion capacity of carbon monoxide – DLco) in addition to spirometry is important because they provide information about disease repercussions on lung function and gas exchanges.

The most common risk factor for COPD is smoking (e.g., cigarette, pipe, and cigar), but there are other factors that should be valued in the disease development context, such as environmental, occupational, and indoor exposure.[1] COPD is traditionally thought to be a male disease, but its prevalence in women in developed countries is increasing[2] since they are adopting lifestyle habits similar to men with regard to tobacco consumption.[3]

The raise of COPD prevalence in women is associated with an increase in smoking habits, but there are other risk factors, which also contribute to a greater susceptibility of female gender to tobacco smoke effects. Aspects, such genetic predisposition, hormonal factors, tobacco smoke components metabolization, anatomical and physiological characteristics, bronchial hyperreactivity, and noxious agents exposure,[4-9] promote inequalities regarding symptomatology, mortality, and lung function decline.[10]

Since COPD is a globally prevalent disease and affects men and women in ever-increasing proportions, it is important to identify and characterize the particularities of tobacco smoke effects in both genders, including lung function inequalities. It was objective of this literature review to characterize the gender susceptibility differences in COPD development as well as the changes that this disease may induce in the lung function.

Methodology

A literature review of publications indexed in MEDLINE, Latindex, SciELO, and DOAJ databases was carried out. Were also included documents from other origins with recognized interest for topic studied. Keywords (individual or conjugated with Boolean operators – AND, OR, and NOT) were used: COPD; gender; susceptibility; lung function; and its equivalents in Portuguese and Spanish. No time limit was set for articles inclusion, opting to use all of those freely available on the internet, and containing relevant content. Original articles, review articles, or other documents that contained important information for the topic were considered. A total of 264 articles were retrieved, of which 88 were excluded because they were not directly topic-related, 27 were repeated, 22 did not present satisfactorily the methodology used, 43 only the abstract was available, and 24 were written in other languages than English, Portuguese, or Spanish. For this review article, 44 sources were considered. Table 1 describes some information about the documents considered.

Susceptibility differences in chronic obstructive pulmonary disease development

The existence of increased susceptibility to tobacco smoke effects in women is described in literature, and multiple aspects that contribute to gender inequalities in COPD development have been identified. These include genetic predisposition, hormonal factors, tobacco smoke components metabolization, anatomical and physiological characteristics, bronchial hyperreactivity, and noxious agent's exposure.

Genetic predisposition is one of the factors that contribute to susceptibility differences in tobacco smoke deleterious effects.[11,12] COPD is a consequence of the combination between genetic predisposition and environmental exposure to harmful agents, and that is the reason for not all individuals with current or past smoking habits to develop this disease.[13]

The α1-antitrypsin deficiency (protein responsible for most of the antiprotease protection of the respiratory system)[14] is considered the most significant genetic factor for COPD development.[4] The phenotypes that confer a seriously increased risk for lung disease development are those with a combination of deficient alleles (Pi and Z) or homozygous or heterozygous nulls, which express α1-antitrypsin below the threshold concentration considered protective. In Brantly *et al*.[4] and Fagerhol *et al*.[15] studies, no differences were found in individuals genotypes with α1-antitrypsin deficiency according to gender; however, Fähndrich *et al*.[5] in their investigation, which included individuals of both genders with α1-antitrypsin deficiency and COPD, found that in all stages of COPD, the female gender had a lower smoking burden than male gender, despite the airflow limitation was similar between them at different disease stages.

Hormonal factors may play an important role in magnitude and characteristics of the inflammatory response of airways and pulmonary parenchyma to tobacco smoke. Based on the hormonal characteristics, female is more susceptible to tobacco smoke effects[16] than male, because estrogen and progesterone are essential in the lung development and lung function.[13]

Cyclic changes in estradiol body concentrations are associated with changes in pulmonary adrenergic receptors density, mucus, acetylcholine, and prostaglandin concentrations. The occurrence of oxidative stress caused by tobacco smoke is more evident

Table 1: Documents information

Author	Year	Title	Article type	Database
GOLD	2019	Global strategy for the diagnosis, management, and prevention of COPD	Guidelines	GOLD
Van Haren-Willems J, Heijdra Y	2010	Increasing evidence for gender differences in COPD	Review article	MEDLINE
Han M, Postma D, Mannino D, *et al*.	2007	Gender and COPD-why it matters	Review article	MEDLINE
Brantly ML, Paul LD, Miller BH, Falk RT, Wu M, Crystal RG	1988	Clinical features and history of the destructive lung disease associated with alpha-1-antitrypsin deficiency of adults with pulmonary symptoms	Original article	MEDLINE
Fähndrich S, Herr C, Greulich T, *et al*.	2015	Sex differences in alpha-1-antitrypsin deficiency lung disease-analysis from the German Registry	Original article	MEDLINE
Scichilone N, Messina M, Battaglia S, Catalano F, Bellia V	2005	Airway hyperresponsiveness in the elderly: prevalence and clinical implications	Original article	MEDLINE
Piccinni MP, Giudizi MG, Biagiotti R, *et al*.	1995	Progesterone favors the development of human T-helper cells producing Th2-type cytokines and promotes both interleukin-4 production and membrane CD30 expression in established Th1 cell clones	Review article	MEDLINE
Manfreda J, Sears MR, Becklake MR, *et al*.	2004	Geographic and gender variability in the prevalence of bronchial responsiveness in Canada	Original article	MEDLINE
Anthonisen N, Connett J, Murray R	2002	Smoking and lung function of lung health study participants after 11 years	Original article	MEDLINE
Pereira P, de Sousa M, Barros R	2003	Characterization of carbon monoxide diffusion capacity and partial pressure of oxygen in arterial blood in COPD patients	Original article	DOAJ
Cote, CG, Chapman, *et al*.	2009	Diagnosis and treatment considerations for women with COPD	Review article	MEDLINE
Silverman EK, Weiss ST, Drazen JM, *et al*.	2000	Gender-related differences in severe, early-onset COPD	Original article	MEDLINE
Greaves L, Richardson L	2007	Tobacco use, women, gender, and COPD are the connections being adequately made	Review article	MEDLINE
Cardoso P	2009	Alpha-1-antitrypsin in chronic obstructive pulmonary disease	Master degree monography	Coimbra University-Master Degree monography
Fagerhol MK, Laurell CB	1967	The polymorphism of “prealbumins” and alpha-1-antitrypsin in human sera	Review article	MEDLINE
Olivieri O, Girelli D, Stanzial AM, Rossi L, Bassi A, Corrocher R	1996	Selenium, zinc, and thyroid hormones in healthy controls: Low T3/T4 ratio in the elderly is related to impaired selenium status	Original article	MEDLINE
Becklake M, Kauffmann F	1999	Gender differences in airway behavior over the human life span	Review article	MEDLINE
Benowitz N, Hukkanen J, Jacob P 3rd	2009	Nicotine chemistry, metabolism, kinetics, and biomarkers	Review article	MEDLINE
Martinez F, Curtis J, Sciurba F *et al*.	2007	Sex differences in severe pulmonary emphysema	Original Article	MEDLINE
Kelly RW, Illingworth P, Baldie G, Leask R, Brouwer S, Calder AA	1994	Progesterone control of interleukin-8 production in endometrium and choriodecidual cells underlies the role of the neutrophil in menstruation and parturition	Review article	MEDLINE
Caracta CF	2003	Gender differences in pulmonary disease	Review article	MEDLINE
Paoletti P, Carrozzi L, Viegi G, *et al*.	1995	Distribution of bronchial responsiveness in a general population: Effect of sex, age, smoking, and level of pulmonary functions	Original article	MEDLINE
Rubinstein M, Shiffman S, Rait M, Benowitz N	2013	Race, gender, and nicotine metabolism in adolescent smokers	Original article	MEDLINE
Uppstad H, Osnes GH, Cole KJ, Phillips DH, Haugen A, sMollerup S	2011	Sex differences in susceptibility to PAHs is an intrinsic property of human lung adenocarcinoma cells	Original article	MEDLINE
Benowitz NL, Lessov-Schlaggar CN, Swan GE, Jacob P 3rd	2006	Female sex and oral contraceptive use accelerate nicotine metabolism	Original article	MEDLINE

Contd...

Table 1: Contd...

Author	Year	Title	Article type	Database
Berlin I, Gasior M, Moolchan E	2007	Sex-based and hormonal contraception effects on the metabolism of nicotine among adolescent tobacco-dependent smokers	Original article	MEDLINE
Barnes P	2016	Sex differences in COPD mechanisms	Editorial	MEDLINE
Kim Y, Schroeder J, Lynch D, *et al*.	2011	Gender differences of airway dimensions in anatomically-matched sites on CT in smokers	Original article	MEDLINE
Grootendorst D, Rabe K	2004	Mechanisms of bronchial hyperreactivity in asthma and COPD	Review article	MEDLINE
Wise RA, Enright PL, Connett JE, *et al*.	1998	Effect of weight gain on pulmonary function after smoking cessation in the lung health study	Original article	MEDLINE
Kanner RE, Connett JE, Altose MD, *et al*.	1994	Gender difference in airway hyperresponsiveness in smokers with mild COPD: The lung health study	Original article	MEDLINE
Wang X, Mensinga T, Schouten J, Rijcken B, Weiss S	2004	Determinants of maximally attained level of pulmonary function	Original article	MEDLINE
Prescott E, Bjerg AM, Andersen PK, Lange P, Vestbo J	1997	Gender difference in smoking effects on lung function and risk of hospitalization for COPD: Results from a Danish longitudinal study	Original article	MEDLINE
Birring SS, Brightling CE, Bradding P, *et al*.	2002	Clinical, radiologic, and induced sputum features of COPD in nonsmokers: A descriptive study	Original article	MEDLINE
Machado MC, Krishnan JA, Buist SA, *et al*.	2006	Sex differences in survival of oxygen-dependent patients with COPD	Original article	MEDLINE
Varkey AB	2004	COPD in women: Exploring gender differences	Review article	MEDLINE
Fernandes L, Mesquita A	2014	Understanding gender differences in the clinical presentation of COPD: A cross-sectional study	Original article	Scielo
Pandey MR	1984	Domestic smoke pollution and chronic bronchitis in a rural community of the Hill Region of Nepal	Original article	MEDLINE
Langhammer A, Johnsen R, Holmen J, Gulsvik A, Bjermer L	2000	Cigarette smoking gives more respiratory symptoms among women than among men the HUNT	Original article	MEDLINE
Sørheim IC, Johannessen A, Gulsvik A, Bakke PS, Silverman EK, DeMeo DL	2010	Gender differences in COPD: Are women more susceptible to smoking effects than men	Original article	MEDLINE
Trigo JM, Báron A	2005	Valoración funcional del paciente con EPOC	Review article	Latindex
Guenette JA, Jensen D, Webb KA, Ofir D, Raghavan N, O'Donnell DE	2011	Sex differences in exertional dyspnea in patients with mild COPD: Physiological mechanism	Original article	MEDLINE
Nakano Y, Sakai H, Muro S, *et al*.	1999	Comparison of low attenuation areas on computed tomographic scans between inner and outer segments of the lung in patients with COPD: Incidence and contribution to lung functions	Original article	MEDLINE
Balcells E, Antó JM, Gea J, *et al*.	2009	Characteristics of patients admitted for the first time for COPD exacerbation	Original article	Latindex

GOLD: Global Initiative for Chronic Obstructive Lung Disease, COPD: Chronic obstructive pulmonary disease, HUNT: Nord-Trondelag health study, CT: Computed tomography, CD: Cluster differentiation, DOAJ: Directory of Open Access Journals

in female compared to male, which justifies a greater susceptibility of women to smoking effects.[17] The metabolism of chemical substances present in tobacco smoke is mediated by cytochrome P450 (CYP) enzymes, which are regulated by estradiol. These enzymes are responsible for the transformation of harmful compounds into intermediate metabolites. These metabolites must be excreted to eliminate them from the body, but when this does not happen they accumulate in the lung, and due to their toxicity, they will cause an oxidizing effect through a process called bioactivation.[18] Since estradiol concentrations are related to cytochrome enzymes concentrations,[19] it can be inferred that this female hormone is linked to oxidative stress that occurs at pulmonary level and consequently to the appearance of airway lesion.

Progesterone is related to the inflammatory process, inducing cyclical changes in interleukin 8 production[7] (IL-8-main mediator of immune response).[20] According to Caracta,[21] the tobacco smoke inhalation promotes the increase of IL-8 levels, which attract neutrophils, originating airway inflammatory response, and promoting the development of bronchial obstruction typical of COPD.

Another factor (which is potentially related to gender hormonal differences) that may contribute to men and

women tobacco smoke effects differences on the airways and pulmonary parenchyma is the way that tobacco compounds are metabolized[6-8,22] Due to the hormones, female metabolizes nicotine more quickly than male. Estrogen can affect the activity of CYP2A6 enzyme (the primary enzyme responsible for nicotine metabolism for cotinine)[23] and also justifies why women have a longer exposure to noxious particles.[24] According to Benowitz *et al*.,[25] in addition to metabolization differences between genders, there are discrepancies into female gender, especially in women who use oral contraceptives that include estrogen, so the authors emphasize the influence of hormonal factors in tobacco smoke substances clearance. Berlin *et al*.[26] carried out a study which aimed to compare nicotine metabolism among adolescents of both genders and the influence of regular use of hormonal contraceptives on nicotine and cotinine metabolism. The investigation included 120 adolescents, in which the plasma concentrations of nicotine and cotinine were analyzed. No differences were found between genders, with similar results in girls and boys in plasma nicotine and plasma cotinine; however, differences were found regarding 3HC-cotinine ratios, because girls presented higher levels than boys. After stratifying girls into two groups based on the use versus nonuse of hormonal contraception, plasma 3HC-cotinine ratios in girls using hormonal contraception were substantially higher than boys and were significantly higher than girls not using hormonal contraception ($P < 0.0001$). That study showed that hormonal contraception in adolescent girls may accelerate cotinine metabolism, an effect likely related to induction of CYP P4502A6.

Concerning the effects of hormonal contraception, Rubinstein *et al*.[23] did not obtain significant differences in nicotine metabolism ratio among 19 women who reported using estrogen-containing contraceptives versus 83 nonusers ($P = 0.24$) or 10 women using contraceptives only with progesterone ($P = 0.45$). The nicotine metabolism variety can be attributed to enzymatic activity variability of CYP2A6, being ≥50% hereditary,[23] affecting CYP2A6 activity, including genetic polymorphisms.[23]

According to Barnes,[27] the idea that female gender hormones may contribute for greater COPD susceptibility were explored in a mouse model exposed to chronic cigarette smoke. Female animals developed more evident small airway remodeling and peripheral airway obstruction than male animals, who developed predominantly emphysema. Ovariectomy produced the same pattern as male mice, indicating that female hormones were responsible for these differences. Furthermore, the estrogen receptor-α blocker tamoxifen mimicked the effects of ovariectomy, indicating that estrogen contributes for gender differences in chronic smoking response.

The anatomical and physiological characteristics of individuals can influence the onset, progression, and response to therapy of COPD. In order to evaluate the lung damage from smoking, computed tomography (CT) scan is a valuable tool. Although CT scan measurements of airway dimensions are predominantly of medium-sized, they could be representative of remodeling degree in small airways.[27] According to Kim *et al*.,[28] it is possible to prove that genders differ in airways size, being that majority of airway measurements (internal diameter, wall thickness, and lumen area) lower in women compared to men ($P < 0.001$) and women presented higher wall area percentage (WA%) in subsegmental and subsubsegmental bronchi ($P < 0.001$). Having women smaller airways, the concentration of tobacco smoke is higher, resulting in increased exposure to the substance, which leads to increased susceptibility for disease development.[6-8,22] The significant luminal area reduction in women is particularly important to physiology, because smaller size of women's lungs is associated with lower flow rates.[28] Furthermore, airflow limitation in COPD is more closely related to dimensions of distal airways than proximal airways. The smaller lumen area and the higher WA% of distal airways in women could explain why they have a higher COPD development susceptibility and may also explain gender differences in disease presentation of airflow obstruction. It is possible to conclude that female smokers have disproportionately higher WA%, but lower luminal area and airway thickness in anatomically matched sites, subsegmental and subsubsegmental bronchi as measured by CT scan than male smokers. These aspects may explain gender differences in COPD heterogeneity and airflow obstruction.[28] Boys and girls of the same age may be at different stages of respiratory system maturation and express different vulnerabilities to harmful substances such as tobacco smoke, because of that the early onset of smoking habits has a greater negative impact on lung function development of females than males, which may represent a favorable factor for the early COPD onset.[13]

Bronchial hyperreactivity is defined as an exaggerated bronchoconstriction response of the airways to certain inhaled stimuli.[29] According to Grootendorst and Rabe,[29] 30%–40% of smokers and 18%–25% of ex-smokers without airway obstruction have bronchial hyperreactivity, which indicates that smoking is a risk factor for COPD development and progression.[29,30] Female has a greater bronchial hyperreactivity, which manifests in a more responsive base to methacholine than male,[31] this hyperreactivity is directly related to smaller airway caliber,[32,33] reason why the women are more predisposed to develop lung function impairment induced by smoking.[18,33-35]

Literature portrays an association between biomass exposure and COPD development.[36] Depending on the country where they live and the sociocultural environment where individuals are inserted; environmental, occupational, and indoor exposure factors seem to influence susceptibility differences between genders. The study of Fernandes and Mesquita[37] conducted in developing country shows the relevance of exposure type in COPD development, particularly the importance in female gender of indoor pollution, resulting from burning fuels such as coal and biomass used for cooking and heating. Pandey[38] verified a higher prevalence of chronic bronchitis in female gender and a statistically significant correlation ($P < 0.05$) with indoor exposure. These results cannot be explained by smoking habits since most women included in the study were nonregular smokers. In developed countries, the difference in gender susceptibility, related to the type of exposures mentioned above, is increasingly faded, because the genders are increasingly assimilated at professional and sociocultural level.[3,12] The existence of protection policies of citizens from involuntary tobacco smoke exposure and demand-reduction measures related to dependence and cessation of consumption[14] contribute to exposure reduction to environmental, occupational, and indoor risk factors that promote COPD and for the similarities between men and women.

Chronic obstructive pulmonary disease - lung function tests and gender

Smoking is the main cause of COPD in both genders,[39,40] but the findings about the differences between men and women relatively to deleterious effects of tobacco smoke on lung function remain controversial, and there is no consensus on this issue.

The female gender susceptibility to tobacco smoke is described in the literature in studies such as those performed by Prescott *et al*.[33] and Langhammer *et al*.,[39] which revealed that female, even with less expressive smoking habits suffers from a greater lung function impairment than male. The study of Prescott *et al*.,[33] which aimed to analyze gender and smoking interaction in COPD development, included 13,897 individuals from two population studies, 9083 from the Copenhagen City Heart Study (CCHS) and 4814 from Glostrup Population Studies (GPS). The men had a greater environmental exposure to tobacco smoke, smoking burden, deep inhalation of tobacco smoke, and an earlier age of tobacco consumption onset than women ($P < 0.05$). Despite the above, it was observed that the largest lung functional decline per pack/year occurred in female, having obtained a decline in the CCHS sample of 7.4 mL and the GPS sample of 10.5 mL, and men was observed a decline of 6.3 mL and 8.1 mL, respectively ($P < 0.05$). The study by Langhammer *et al*.[39] included a sample of 65,225 individuals from the Nord-Trøndelag Health Study and 10,941 from the Bronchial Obstruction in Nord-Trøndelag study and found that female gender despite a significant lower smoking burden than male gender (11.5 pack/years vs. 15.5 pack/years, $P < 0.01$) presented a greater lung functional decline per pack/year. Regarding FVC and FEV_1, women presented a decline of 0.52% and 0.28% and men of 0.32% and 0.16%, respectively ($P < 0.001$).

In order to understand the effects of harmful particles exposure in lung function in both genders, some authors have used different methodologies than those reported in the previous studies since they quantified the percentage value of lung functional parameters and not the rate of decline according to pack/years.

The research developed by Sørheim *et al*.[40] aimed to study how smoking affects the lung function according to gender and included 954 individuals with COPD who were divided into two groups: individuals under 60 years (early-onset group) and individuals with pack/years below 20 (low exposure group). In early-onset group, it was observed that men had a statistically higher mean of pack/years and occupational exposure to harmful substances than women (28.4 pack/years vs. 24.0 pack/years, $P = 0.003$) and (81.2% vs. 51.2%, $P < 0.001$). In low exposure group, there were no statistically significant differences between genders relative to pack/years ($P > 0.05$); however, it was observed that men were statistically more exposed at the occupational level than women (55.8% vs. 48.7%; $P = 0.001$). In early-onset group (FEV_1 - male: 56.0% vs. female: 50.6%) and the low exposure group (FEV_1-male: 55.8% vs. female: 48.7%), women presented a further reduction in FEV_1, with differences between the genders being statistically significant ($P < 0.05$). The differences found between genders in studied groups suggest that female gender is associated with worse lung function and greater COPD severity degree. The authors report that women tolerate tobacco smoke less well than men and consequently experience a higher level of lung impairment at a younger age, even with low substance exposure.

The investigations presented previously evaluated the lung functional differences between genders in individuals with COPD, only with the use of spirometry, but for a deeper characterization of the disease, the use of additional techniques (whole-body plethysmography and DLco) has an added value. In COPD, with the progress of pulmonary parenchymal destruction, the lung's elastic retraction capacity reduces, which results in the increase of air contained in distal air spaces at the end of expiration and may eventually manifest itself as

air trapping or pulmonary hyperinflation.[41] In COPD, exists gas exchanges impairment, because emphysema promotes loss of alveoli and reduction of capillary bed, resulting in a smaller area available for diffusion, which is reflected by a decreased DLco.[42]

The study by Guenette *et al*.[42] included 32 individuals of both genders and aimed to assess the physiological basis of gender differences in exercise-induced dyspnea in patients with mild COPD. The patients did not present statistically significant differences regarding smoking habits ($P > 0.05$). From spirometry analysis, no statistically significant differences were detected in FEV_1 or FVC ($P > 0.05$) between genders. Whole-body plethysmography did not show statistically significant differences in functional residual capacity or total lung capacity (TLC) ($P > 0.05$), but these differences gained significance in residual volume (RV) (men: 128.0% vs. women: 114.0%, $P < 0.05$). Relatively of DLco, there were no statistically significant differences between genders ($P > 0.05$). In this investigation, spirometry and DLco did not reveal gender differences; however, whole-body plethysmography revealed that male gender had higher VR than female gender, which means that men have a higher volume of air inside lungs after maximum expiration. In this study, data from imaging techniques were not presented, so it is not possible to know the predominance of chronic bronchitis or emphysema in each individual, information that would be important for results interpretation.

The investigation of Martinez *et al*.[19] aimed to compare men and women with severe emphysema and included a total of 1053 individuals from the National Emphysema Treatment Trial, who underwent lung function tests and thorax CT scan. It was found that men had a significantly higher smoking burden than women (71.1 pack/years vs. 54.8 pack/years, $P = 0.0001$) and started smoking at an early age (16.0 years vs. 17.7 years, $P < 0.0001$). Through the CT scan, it was possible to observe that women had less extensive emphysema, less emphysema, and less peripheral involvement. In spirometry, it was found that men had a statistically lower mean of FEV_1 than women (25.9% vs. 29.0%, $P < 0.0001$), in whole-body plethysmography, there were no differences between the genders ($P > 0.05$) and in DLco, women had a statistically lower mean of this parameter than men (27.2% vs. 29.3%, $P = 0.0005$). It was found that although women presented less severe emphysema, they obtained an average of DLco lower than men, which would not be expected, this aspect may be related to the complex contributions of pulmonary mechanics and gas exchanges that influence DLco. There are studies that have identified differences in the impact of emphysema distribution (central or peripheral) on DLco,[43] so the distribution of emphysema identified in women may explain the differences in DLco found between genders. Although they had a lower exposure to tobacco smoke, women had an FEV_1 mean similar to men, what does it mean that they presented a similar airway obstruction severity, which is indicative of the presence of higher degree of airway disease in peripheral areas, which was confirmed by performing a subanalysis that included individuals of both genders with airflow obstruction and similar smoking history, and it was confirmed that women had lower lumen of airways and bronchial walls thicker than men. Since this study only included patients with severe bronchial obstruction, the authors do not exclude the possibility that lung function deteriorates more rapidly in women at milder stages of disease.

The study of Balcells *et al*.[44] included 318 men and 24 women, who were admitted to the emergency room for the first time due to COPD exacerbation. Lung functional assessment was only performed after clinical stability. Through the analysis of data, it was possible to verify that male gender had statistically lower mean of FVC (67.9%) and FEV_1 (48.1%) ($P = 0.002$ and $P = 0.015$) than female gender (78.7% and 56.0%). No statistically significant differences were detected in RV/TLC ratio and DLco ($P > 0.05$). Regarding patients distribution by COPD severity degrees, it was observed that the majority of individuals (in both genders) were included in moderate stage of disease (men: 46.9% vs. women: 62.5%). This investigation did not find a greater susceptibility of female gender to the effects of tobacco smoke on lung function; however, these results should be interpreted taking into account the specificities of this investigation, namely the great asymmetry of the sample regarding the gender, only individuals with <45 years of age were studied, and no data about patients smoking habits were provided, which may have conditioned the results and made it difficult to compare them with those obtained in other studies.

Final considerations

It was possible to verify through the present literature review, the multiplicity of factors that potentially influence the susceptibility differences between genders for COPD development. This aspect makes this theme of great complexity what is revealed when studying the effects of harmful particles exposure in the lung function. It could be observed that there is a great variability of results regarding lung functional differences between men and women with COPD, what it means that there is no consensus about the existence of a more pronounced lung functional loss by the female gender. However, it is important to point out that there are great methodological and population asymmetries in the investigations presented what makes difficult the interpretation and comparison of

results. For the reasons above, it is fundamental to develop further studies on this patient to clarify the specificities of the effects of noxious particles exposure in the lung function, particularly how it affects men or women.

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Conflicts of interest

There are no conflicts of interest.

References

1. Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: The GOLD science committee report 2019. Eur Respir J 2019;53. pii: 1900164.
2. van Haren-Willems J, Heijdra Y. Increasing evidence for gender differences in chronic obstructive pulmonary disease. Womens Health (Lond) 2010;6:595-600.
3. Han MK, Postma D, Mannino DM, Giardino ND, Buist S, Curtis JL, *et al.* Gender and chronic obstructive pulmonary disease: Why it matters. Am J Respir Crit Care Med 2007;176:1179-84.
4. Brantly ML, Paul LD, Miller BH, Falk RT, Wu M, Crystal RG. Clinical features and history of the destructive lung disease associated with alpha-1-antitrypsin deficiency of adults with pulmonary symptoms. Am Rev Respir Dis 1988;138:327-36.
5. Fähndrich S, Herr C, Greulich T, Seibert M, Lepper PM, Bernhard N, *et al.* Sex differences in alpha-1-antitrypsin deficiency lung disease-analysis from the German registry. COPD 2015;12 Suppl 1:58-62.
6. Scichilone N, Messina M, Battaglia S, Catalano F, Bellia V. Airway hyperresponsiveness in the elderly: Prevalence and clinical implications. Eur Respir J 2005;25:364-75.
7. Piccinni MP, Giudizi MG, Biagiotti R, Beloni L, Giannarini L, Sampognaro S, *et al.* Progesterone favors the development of human T helper cells producing Th2-type cytokines and promotes both IL-4 production and membrane CD30 expression in established Th1 cell clones. J Immunol 1995;155:128-33.
8. Manfreda J, Sears MR, Becklake MR, Chan-Yeung M, Dimich-Ward H, Siersted HC, *et al.* Geographic and gender variability in the prevalence of bronchial responsiveness in Canada. Chest 2004;125:1657-64.
9. Anthonisen NR, Connett JE, Murray RP. Smoking and lung function of lung health study participants after 11 years. Am J Respir Crit Care Med 2002;166:675-9.
10. Pereira P, de Sousa M, Barros R. Characterization of carbon monoxide diffusion capacity and partial pressure of oxygen in arterial blood in COPD patients. 2013. Salutis Sci 2003;5:9-21.
11. Cote CG, Chapman KR. Diagnosis and treatment considerations for women with COPD. Int J Clin Pract 2009;63:486-93.
12. Silverman EK, Weiss ST, Drazen JM, Chapman HA, Carey V, Campbell EJ, *et al.* Gender-related differences in severe, early-onset chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000;162:2152-8.
13. Greaves LJ, Richardson LA. Tobacco use, women, gender, and chronic obstructive pulmonary disease: Are the connections being adequately made? Proc Am Thorac Soc 2007;4:675-9.
14. Cardoso P. Alpha-1-antitrypsin in chronic obstructive pulmonary disease. Coimbra University; 2009.
15. Fagerhol MK, Laurell CB. The polymorphism of "prealbumins" and alpha-1-antitrypsin in human sera. Clin Chim Acta 1967;16:199-203.
16. Olivieri O, Girelli D, Stanzial AM, Rossi L, Bassi A, Corrocher R, *et al.* Selenium, zinc, and thyroid hormones in healthy subjects: Low T3/T4 ratio in the elderly is related to impaired selenium status. Biol Trace Elem Res 1996;51:31-41.
17. Becklake MR, Kauffmann F. Gender differences in airway behaviour over the human life span. Thorax 1999;54:1119-38.
18. Benowitz NL, Hukkanen J, Jacob P 3rd. Nicotine chemistry, metabolism, kinetics and biomarkers. Handb Exp Pharmacol 2009;(192):29-60.
19. Martinez FJ, Curtis JL, Sciurba F, Mumford J, Giardino ND, Weinmann G, *et al.* Sex differences in severe pulmonary emphysema. Am J Respir Crit Care Med 2007;176:243-52.
20. Kelly RW, Illingworth P, Baldie G, Leask R, Brouwer S, Calder AA. Progesterone control of interleukin-8 production in endometrium and chorio-decidual cells underlines the role of the neutrophil in menstruation and parturition. Hum Reprod 1994;9:253-8.
21. Caracta CF. Gender differences in pulmonary disease. Mt Sinai J Med 2003;70:215-24.
22. Paoletti P, Carrozzi L, Viegi G, Modena P, Ballerin L, Di Pede F, *et al.* Distribution of bronchial responsiveness in a general population: Effect of sex, age, smoking, and level of pulmonary function. Am J Respir Crit Care Med 1995;151:1770-7.
23. Rubinstein ML, Shiffman S, Rait MA, Benowitz NL. Race, gender, and nicotine metabolism in adolescent smokers. Nicotine Tob Res 2013;15:1311-5.
24. Uppstad H, Osnes GH, Cole KJ, Phillips DH, Haugen A, Mollerup S, *et al.* Sex differences in susceptibility to PAHs is an intrinsic property of human lung adenocarcinoma cells. Lung Cancer 2011;71:264-70.
25. Benowitz NL, Lessov-Schlaggar CN, Swan GE, Jacob P 3rd. Female sex and oral contraceptive use accelerate nicotine metabolism. Clin Pharmacol Ther 2006;79:480-8.
26. Berlin I, Gasior MJ, Moolchan ET. Sex-based and hormonal contraception effects on the metabolism of nicotine among adolescent tobacco-dependent smokers. Nicotine Tob Res 2007;9:493-8.
27. Barnes PJ. Sex differences in chronic obstructive pulmonary disease mechanisms. Am J Respir Crit Care Med 2016;193:813-4.
28. Kim YI, Schroeder J, Lynch D, Newell J, Make B, Friedlander A, *et al.* Gender differences of airway dimensions in anatomically matched sites on CT in smokers. COPD 2011;8:285-92.
29. Grootendorst DC, Rabe KF. Mechanisms of bronchial hyperreactivity in asthma and chronic obstructive pulmonary disease. Proc Am Thorac Soc 2004;1:77-87.
30. Wise RA, Enright PL, Connett JE, Anthonisen NR, Kanner RE, Lindgren P, *et al.* Effect of weight gain on pulmonary function after smoking cessation in the lung health study. Am J Respir Crit Care Med 1998;157:866-72.
31. Kanner RE, Connett JE, Altose MD, Buist AS, Lee WW, Tashkin DP, *et al.* Gender difference in airway hyperresponsiveness in smokers with mild COPD. The lung health study. Am J Respir Crit Care Med 1994;150:956-61.
32. Wang X, Mensinga TT, Schouten JP, Rijcken B, Weiss ST. Determinants of maximally attained level of pulmonary function. Am J Respir Crit Care Med 2004;169:941-9.
33. Prescott E, Bjerg AM, Andersen PK, Lange P, Vestbo J. Gender difference in smoking effects on lung function and risk of hospitalization for COPD: Results from a Danish longitudinal population study. Eur Respir J 1997;10:822-7.
34. Birring SS, Brightling CE, Bradding P, Entwisle JJ, Vara DD, Grigg J, *et al.* Clinical, radiologic, and induced sputum features of chronic obstructive pulmonary disease in nonsmokers: A descriptive study. Am J Respir Crit Care Med 2002;166:1078-83.
35. Machado MC, Krishnan JA, Buist SA, Bilderback AL, Fazolo GP, Santarosa MG, *et al.* Sex differences in survival of oxygen-dependent patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2006;174:524-9.

36. Varkey AB. Chronic obstructive pulmonary disease in women: Exploring gender differences. Curr Opin Pulm Med 2004;10:98-103.
37. Fernandes L, Mesquita A. Understanding gender differences in the clinical presentation of chronic obstructive pulmonary disease: A cross-sectional study. Int J Med Sci Public Health 2014;3:1173-7.
38. Pandey MR. Domestic smoke pollution and chronic bronchitis in a rural community of the hill region of Nepal. Thorax 1984;39:337-9.
39. Langhammer A, Johnsen R, Holmen J, Gulsvik A, Bjermer L. Cigarette smoking gives more respiratory symptoms among women than among men. The Nord-Trondelag health study (HUNT). J Epidemiol Community Health 2000;54:917-22.
40. Sørheim IC, Johannessen A, Gulsvik A, Bakke PS, Silverman EK, DeMeo DL. Gender differences in COPD: Are women more susceptible to smoking effects than men? Thorax 2010;65:480-5.
41. Trigo J.M, Báron A. Functional evaluation of patients with COPD. Arch Bronconeumol 2005;41:18-23.
42. Guenette JA, Jensen D, Webb KA, Ofir D, Raghavan N, O'Donnell DE. Sex differences in exertional dyspnea in patients with mild COPD: Physiological mechanisms. Respir Physiol Neurobiol 2011;177:218-27.
43. Nakano Y, Sakai H, Muro S, Hirai T, Oku Y, Nishimura K, *et al.* Comparison of low attenuation areas on computed tomographic scans between inner and outer segments of the lung in patients with chronic obstructive pulmonary disease: Incidence and contribution to lung function. Thorax 1999;54:384-9.
44. Balcells E, Antó JM, Gea J, Gómez FP, Rodríguez E, Marin A, *et al.* Characteristics of patients admitted for the first time for COPD exacerbation. Respir Med 2009;103:1293-302.