



COPD in women: susceptibility or vulnerability?

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Women are both more susceptible and more vulnerable than men when it comes to COPD
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The concepts of susceptibility and vulnerability are intertwined because vulnerability is sometimes a consequence of being susceptible. Women are more likely to be susceptible to chronic obstructive pulmonary disease (COPD) than men [1]. As many women continue to smoke during pregnancy, the impact of tobacco in women can begin before birth [2], because maternal smoking during pregnancy may increase the risk of childhood respiratory diseases [3] and reduce lung function [2]. Indeed, this susceptibility starts before women become smokers. For example, women with specific genotype variants are at a significantly increased risk of becoming heavy smokers [4], while those women with the haplotype TAS2R38 (proline-alanine-valine) have a genetic propensity to experience heightened bitter taste perception and an increased preference for menthol cigarettes [5]. Recent findings of the Global Youth Tobacco survey on adolescents aged 13–15 years showed that young girls smoke as much as young boys [6]. The early onset of smoking may have a greater deleterious impact on lung function among girls [7] because their lungs are smaller than those of males. Accordingly, the same exposure to a given number of cigarettes smoked can lead to more deleterious effects in women [8]. In this regard, once young females become smokers, addiction may be reinforced by both nicotine and the sensory and social contexts of smoking. Motivations associated with gender can provoke women to have different cues for smoking compared with males [9]; therefore, women are more vulnerable to the social context of smoking and can easily become involved in the nicotine addictive process, along with consequent disease risks.

However, the risk for COPD in women has been associated with both gender and sex biology. For instance, biomass exposure associated to COPD has been linked to gender [10] and the levels of oestrogen [8], and thus to sex biology, as in tobacco smoking. Sex differences associated with oestrogen trigger a search for femininity and body image in young women, and this search is exploited by tobacco companies. These companies sponsor promotions in which public smoking is portrayed by attractive models and movie stars to associate tobacco use with glamour, which more easily targets young women [11]. In young women, oestrogen induces lung differentiation and maturation [8]. However, by the age of menopause, levels of oestrogen and progesterone decline, and there is an important loss of lung function and reduced forced expiratory volume in 1 s (FEV₁) that are associated with smoking [8].

Approximately 20% of the smoking population worldwide are women [6]. This estimate has modified overall vital statistics by increasing the COPD prevalence for women and increasing the frequency of deaths due to COPD [12, 13]. A recent analysis of mortality across three time-periods (1959–1965, 1982–1988 and 2000–2010) showed that the risk of death from cigarette smoking has continually increased among women [14], and the relative risk of death from COPD is now nearly identical for men and women (relative risk of 25 and 27.8 for women and men, respectively) [15].

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The similar mortality rate among men and women can be explained by a rapid deterioration of women once they begin smoking, suggesting a differential propensity for the damaging effects of tobacco smoke. For example, although cross-sectional studies have shown that, at all stages of COPD severity, men have more emphysema than women, as measured by computed tomography (CT) scan [16], the annual decline in lung density (emphysema) is more rapid in women [17]. Similarly, PRESCOTT *et al.* [18] estimated the effects of smoking on lung function and consistently detected greater loss of FEV₁ per pack-year of smoking in women compared with men. Similarly, a more recent meta-analysis of the annual rate of decline in FEV₁ in men and women showed that female current smokers had, with increasing age, a significantly faster annual decline in per cent predicted FEV₁ compared with male current smokers [19]. Both the greater velocity of the FEV₁ decline and worsening emphysema have clinical consequences. In the PLATINO (Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar) study [20], currently smoking females with COPD had more severe obstruction compared with males who had similar cigarette exposure. However, when comparing the sexes among subjects with COPD, females smoked less than males, but 63% of women compared with 44% of males reported a modified Medical Research Council dyspnoea score ≥ 2 . Additionally, a general health status report of fair-to-poor was significantly more common in women. A poorer quality of life has been reported more frequently in females than in males with COPD [21], along with more hospitalisations [18] and exacerbations despite having a similar FEV₁, better oxygenation, better arterial carbon dioxide tension and fewer comorbidities [22].

In 1998, in a study of the epidemiology and genetics of cases with severe, early-onset COPD without severe α_1 -antitrypsin deficiency, SILVERMAN *et al.* [1] detected an unexpected prevalence of 79.6% for females. 2 years later, by expanding their sample size from 44 original families to 84 early-onset COPD families, the researchers showed that first-degree female relatives were more likely to have a >40% reduction in FEV₁ than first-degree male smoking relatives, which suggested that women may be more susceptible to developing severe COPD [23]. More recently, a study by FOREMAN *et al.* [24] re-defined severe, early-onset COPD as a FEV₁/forced vital capacity ratio <0.70 and FEV₁ postbronchodilator <50% in subjects <55 years of age, and enrolled 70 subjects. Among these subjects, 66% were women. Notably, the group with severe, early-onset COPD, compared with older subjects with COPD, had significantly less cumulative tobacco exposure measured as pack-years of smoking. This finding suggests that tobacco smoking was not a primary factor for the development of early-onset COPD and that additional factors were also involved. These factors were mainly sex linked, such as genetic determinants, maternal factors and their interactions, which may explain both the appearance of severe, early-onset COPD as well as the onset of smoking and consequent development of COPD in females.

The study by HARDIN *et al.* [25] in the current issue of the *European Respiratory Journal* highlights once again the greater susceptibility of women to the development of COPD. Additionally, convincing findings demonstrated that women with severe emphysema and severe, early-onset COPD and women with Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade IV exhibited similar rates of emphysema to men but were associated with markedly fewer pack-years, illustrating the following aspects of COPD that warrant further study: 1) the advantages and benefits of phenotyping COPD patients; 2) the need for strategies other than FEV₁ to make a diagnosis of COPD; 3) the perspective of gender regarding the public health phenomenon of COPD; and 4) the need for early diagnosis of COPD in smokers, particularly in women smokers, to prevent the late consequences of severe COPD.

HARDIN *et al.* [25] describe at least three phenotypes (early onset COPD, severe emphysema and GOLD grade IV COPD) and suggest the previously reported radiographic emphysema phenotype. According to the work of TATSUMI *et al.* [26], 90% of subjects with COPD have an emphysema-dominant phenotype. Therefore, considering that asymptomatic smokers with COPD have been previously described in subjects with emphysema using lung imaging [27], CT may become the only strategy to detect early COPD. Therefore, although females have an airway disease-dominant phenotype [26, 28], the data of HARDIN *et al.* [25] show that women with early-onset COPD have equivalent emphysema with fewer pack-years of smoking, which should motivate us to incorporate the gender perspective and need for early diagnosis into our clinical practice. Gender selection for the development of COPD may be enhanced by disadvantages encountered during childhood [3, 29].

The study of HARDIN *et al.* [25] also yields insights into which currently used instruments other than FEV₁ should be used to make an early diagnosis and evaluate the severity of COPD. Other investigators who have analysed the progression of COPD have found that FEV₁ is an inconsistent measurement [30] and that the rate of change can be highly variable [31], so it is not a good overall measure of the processes that lead to COPD [32] and is poorly related to mortality [30]. The use of CT as a screening strategy may detect women at risk and aid in the early diagnosis of severe, early-onset COPD. However, this approach may not be cost-effective. Nevertheless, it reminds us of the need for new and less expensive tools for the detection of COPD because emphysema may appear before FEV₁ declines. HARDIN *et al.* [25] highlight the

dilemma of the early onset of severe COPD when no strategies exist to make an early diagnosis of COPD in these women, which is even more problematic if they had been asymptomatic smokers.

When reading this article on women <50 years of age with FEV₁ <50% and similar degrees of emphysema to men, we posit the following open questions. When is this damage initiated? What can we do to prevent it? What can we do to make an earlier diagnosis? Why do women who have the same or lower magnitude of tobacco exposure as men develop more severe airflow limitation and emphysema?

These questions may have been difficult to address and, independently of the reflections of the authors, their results appear to give a dual answer: women are both more susceptible and more vulnerable than men. Understanding the genetic, molecular, social and behavioural mechanisms that underlie these differences will require further research. The extent to which both susceptibility and vulnerability contribute and interact to explain sex and gender differences for COPD development and its severity is also largely unexplored. This paper by HARDIN *et al.* [25] represents an important step towards understanding these important issues.

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