Arch Bronconeumol. 2014;50(8):318–324

ARCHIVOS DE BRONCONEUMOLOGIA

www.archbronconeumol.org

Original Article

# Distribution of Clinical Phenotypes in Patients With Chronic Obstructive Pulmonary Disease Caused by Biomass and Tobacco Smoke☆

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ARTICLE INFO

*Article history:*
Received 18 June 2013
Accepted 19 December 2013
Available online 1 July 2014

*Keywords:*
Chronic obstructive pulmonary disease
Biomass
Tobacco
Phenotypes
Comorbidity

ABSTRACT

*Introduction:* Exposure to biomass smoke is a risk factor for chronic obstructive pulmonary disease (COPD). It is unknown whether COPD caused by biomass smoke has different characteristics to COPD caused by tobacco smoke.
*Objective:* To determine clinical differences between these two types of the disease.
*Methods:* Retrospective observational study of 499 patients with a diagnosis of COPD due to biomass or tobacco smoke. The clinical variables of both groups were compared.
*Results:* There were 122 subjects (24.4%) in the biomass smoke group and 377 (75.5%) in the tobacco smoke group. In the tobacco group, the percentage of males was higher (91.2% vs 41.8%, *P*<.0001) and the age was lower (70.6 vs 76.2 years, *P*<.0001). Body mass index and $FEV_1$% values were higher in the biomass group (29.4±5.7 vs 28.0±5.1, *P*=.01, and 55.6±15.6 vs 47.1±17.1, *P*<.0001, respectively). The mixed COPD-asthma phenotype was more common in the biomass group (21.3% vs 5%, *P*<.0001), although this difference disappeared when corrected for gender. The emphysema phenotype was more common in the tobacco group (45.9% vs 31.9%, *P*=.009). The prevalence of chronic bronchitis, exacerbator phenotypes, the comorbidity burden and the rate of hospital admissions were the same in both groups.
*Conclusion:* Differences were observed between COPD caused by biomass and COPD caused by tobacco smoke, although these may be attributed in part to uneven gender distribution between the groups.


## Distribución de fenotipos clínicos en pacientes con enfermedad pulmonar obstructiva crónica por humo de biomasa y por tabaco

*Palabras clave:*
Enfermedad pulmonar obstructiva crónica
Biomasa
Tabaco
Fenotipos
Comorbilidad

RESUMEN

*Introducción:* La exposición al humo de biomasa es un factor de riesgo para enfermedad pulmonar obstructiva crónica (EPOC). Se ignora si la EPOC por biomasa y por tabaco tienen características diferentes.
*Objetivo:* Buscar diferencias clínicas entre ambos tipos de enfermedad.
*Métodos:* Estudio observacional retrospectivo de 499 pacientes diagnosticados de EPOC por biomasa o por tabaco. Se compararon ambos grupos respecto a variables clínicas.
*Resultados:* Ciento veintidós sujetos (24,4%) fueron clasificados en el grupo de biomasa y 377 (75,5%) en el de tabaco. El porcentaje de varones fue más alto en el grupo de tabaco (91,2% vs 41,8%, p < 0,0001) y la edad resultó inferior en este grupo (70,6 vs 76,2 años, p < 0,0001). Los valores del índice de masa corporal y del $FEV_1$% fueron superiores en el grupo de biomasa (29,4 ± 5,7 vs 28,0 ± 5,1; p = 0,01 y 55,6 ± 15,6 vs 47,1 ± 17,1; p < 0,0001, respectivamente). El fenotipo mixto EPOC-asma fue más prevalente en el grupo biomasa (21,3% vs 5%, p < 0,0001), aunque esta diferencia desapareció al hacer una corrección por sexo. El fenotipo enfisema fue más frecuente en el grupo tabaco (45,9% vs 31,9%, p = 0,009). La prevalencia de los fenotipos bronquitis crónica y exacerbador, el peso de las comorbilidades y la tasa de ingresos hospitalarios fueron equivalentes entre los 2 grupos.
*Conclusión:* Existen diferencias clínicas entre la EPOC por humo de biomasa y por tabaco, aunque podrían ser atribuibles en parte a desigualdades de sexo entre ambos grupos.


☆ Please cite this article as: Golpe R, Sanjuán López P, Cano Jiménez E, Castro Añón O, Pérez de Llano LA. Distribución de fenotipos clínicos en pacientes con enfermedad pulmonar obstructiva crónica por humo de biomasa y por tabaco. Arch Bronconeumol. 2014;50:318–324.
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1579-2129/$ – see front matter 

## Introduction

Although tobacco smoke is widely recognized as the main risk factor for chronic obstructive pulmonary disease (COPD), a relatively high percentage of COPD patients in international studies are never-smokers.[1,2] This proportion is particularly high in developing countries, but it is also significant in Europe. In Spain, the IBERPOC found that 24.3% of COPD patients had never smoked.[3] There are several risk factors for the disease that are unrelated to tobacco smoking, with environmental contamination by biomass smoke in enclosed spaces being one of the most important. Indeed, around half of the world's population is exposed to biomass fuel, suggesting that this may be the most significant risk factor for developing COPD worldwide.[1] Various epidemiological studies, including one performed in Spain, confirm the association between biomass smoke exposure and COPD.[4–6]

It remains unclear if COPD due to biomass smoke and that caused by tobacco smoke have different characteristics. It is unknown whether both types of disease have a similar clinical presentation, whether the natural history of the disease is the same, whether patients have similar comorbid conditions and whether pulmonary and systemic inflammatory patterns are similar.[7]

At present, the term COPD is understood to encompass a series of entities with different characteristics, and the importance of defining clinical phenotypes for the classification of patients into subgroups with varying prognostic and therapeutic implications for the clinical management of patients and the conduct of clinical trials has been emphasized.[8,9]

The working hypothesis of the authors is that tobacco smoke and biomass smoke may produce different biological effects that would give rise to a distinctive clinical presentation in each subtype. Clinical features that may differ between the 2 types could be grouped into phenotypes and determine the need for different treatments. Comorbidities associated with COPD may also be different in each of the groups, since biomass smoke may not have the same effect as tobacco smoke in the development of disorders such as cardiovascular or malignant diseases. The main objective of this study has been to identify clinical differences between patients with COPD caused by tobacco smoke and by exposure to biomass smoke. Specifically, an attempt has been made to determine differences in the prevalence of the various pre-defined clinical phenotypes and in comorbidities between both groups.

## Methods

### *Subjects and Study Design*

This is a descriptive, retrospective study performed in the Pulmonology Department of a university hospital attending a population of 220 000 inhabitants, many of whom live in rural areas in which biomass fuels (mainly wood) are commonly used for cooking and heating. The clinical records of 529 consecutive patients seen in a dedicated clinic in the hospital and diagnosed with COPD between January 2009 and June 2013 were retrospectively reviewed. Subjects were selected from a healthcare database that included patients diagnosed by a pulmonologist as having COPD associated with tobacco use, biomass smoke or alpha-1 antitrypsin deficiency. Inclusion criteria for subjects in this study were age ≥40 years, post-bronchodilator $FEV_1$/FVC ratio <0.70, chronic cough, sputum production or dyspnea, and either a history of tobacco smoking or significant exposure to biomass smoke. Exclusion criteria were alpha-1 antitrypsin deficiency, cystic bronchiectasis or cylindrical bronchiectasis attributed to a cause other than COPD, human immunodeficiency virus infection, concomitant interstitial lung disease, current diagnosis of asthma, history of workplace exposure to inorganic dust or types of smoke other than those produced by burning tobacco or biomass, and parenchymal lung disease associated with previous tuberculosis. The study was approved by the ethics committee of the center (Clinical Research Ethics Committee of Galicia, Registry No. 2012/132).

Accumulated exposure to biomass smoke was difficult to calculate, since it often varied over time. Many patients were exposed during their childhood and youth to smoke in the environment from the traditional kitchens used in the region (open fires in a fireplace). These fireplaces produce more contamination than the ovens and stoves that have generally replaced them in recent decades. Moreover, exposure to smoke is significantly higher in the winter months than the rest of the year and varies from year to year with changing climatic conditions. This, and the retrospective nature of the study, made it impossible to accurately estimate smoke exposure in terms of hours/year. However, a population study carried out in over 5000 subjects showed that cooking for 10 years or more over a wood fire was an independent risk factor for COPD.[10] Considering that the study population used biomass not only for cooking but also for heating, and that the latter use may produce less environmental contamination, a conservative attitude was adopted for the purpose of this study and a history of at least 20 years exposure to biomass smoke beginning in childhood was considered significant. Patients were assigned to 2 groups: (1) tobacco group (consumption history of at least 10 pack years), and (2) biomass group (significant exposure to biomass smoke as previously defined, and no tobacco smoking history). For analytical purposes, subjects with a history of smoking were assigned to group 1, even if there was a remote history of exposure to biomass smoke.

Airflow obstruction severity was classified according to the GOLD criteria, on the basis of post-bronchodilator $FEV_1$, from GOLD 1 to GOLD 4.[11] Patients were categorized into 4 groups (GOLD A–D), according to the combined COPD assessment classification recommended by the GOLD initiative,[11] using the Medical Research Council modified dyspnea scale. The BODEx multidimensional index was calculated for each patient according to their situation on their first visit to the pulmonology clinic. This rating assigns different scores depending on body mass index, degree of airway obstruction, severity of dyspnea and number of severe COPD exacerbations.[12] Patient comorbidities were evaluated according to the Charlson index with no adjustment for age[13] and a specific COPD comorbidity index (COTE).[14]

All patients were classified into 3 mutually exclusive phenotypes, using a modified version of the Spanish COPD classification guidelines (GesEPOC)[9]: (1) chronic bronchitis: cough and sputum production for at least 3 months in 2 consecutive years[15]; (2) emphysema: no habitual cough and expectoration, (2.1) pulmonary emphysema revealed on computed tomography (CT), or (2.2) reduced CO diffusion (TLCO/VA<80%), or (2.3) chest X-ray suggestive of emphysema[16]; and (3) mixed COPD-asthma phenotype (MCAP): 2 major criteria or 1 major criterion and 2 minor criteria, as specified in Table 1.

**Table 1**
Criteria for the Diagnosis of the Mixed COPD-Asthma Phenotype Used in the Study.

| |
|---|
| *Major criteria* |
| Positive post-bronchodilator test with an increase of $FEV_1$ >15% and >400 ml |
| FENO > 40 ppb |
| Personal history of asthma |
| *Minor criteria* |
| Elevated IgE in blood |
| Personal history of atopy |
| Positive post-bronchodilator test with an increase of $FEV_1$ > 12% and >200 ml in at least 2 different measurements |

FENO: fractional exhaled nitric acid.
Adapted from Soler-Cataluña et al.[17]