

Bronchial hyperresponsiveness in women with chronic obstructive pulmonary disease related to wood smoke

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Purpose: Chronic obstructive pulmonary disease (COPD) related to wood smoke exposure is characterized by important inflammation of the central and peripheral airways without significant emphysema. The objective of this study is to describe the bronchial hyperresponsiveness (BHR) level in women with COPD related to wood smoke exposure and to compare it with the BHR in women with COPD related to tobacco smoking.

Materials and methods: Two groups of women with stable COPD were studied: (1) wood smoke exposed (WS-COPD); and (2) tobacco smoke exposed (TS-COPD). A methacholine challenge test (MCT) was performed in all patients according to American Thoracic Society criteria. BHR levels were compared using the methacholine concentration, which caused a 20% fall in the FEV₁ (PC₂₀).

Results: Thirty-one patients, 19 with WS-COPD and 12 with TS-COPD, were included. There were no significant differences between the groups in baseline FVC, FEV₁, IC, FEF₂₅₋₇₅, and FEF₂₅₋₇₅/FVC. All 31 patients had a positive MCT (PC₂₀ < 16 mg/mL) and the fall in the FEV₁ and IC was similar in both groups. The severity of BHR was significantly higher in the WS-COPD patients (PC₂₀: 0.39 mg/mL) than in the TS-COPD patients (PC₂₀: 1.24 mg/mL) ($P = 0.028$). The presence of cough, phlegm, and dyspnea during the test were similar in both groups.

Conclusion: We found moderate to severe BHR in women with WS-COPD, which was more severe than in the TS-COPD women with similar age and airflow obstruction. This paper suggests that the structural and inflammatory changes induced by the chronic exposure to wood smoke, described in other studies, can explain the differences with TS-COPD patients. Future studies may clarify our understanding of the impact of BHR on COPD physiopathology, phenotypes, and treatment strategies.

Keywords: biomass fuels, indoor air pollution, wood smoke, COPD, methacholine challenge test

Introduction

Fifty percent of the world population, approximately three billion people, use solid fuels (charcoal or biomass materials) as their main or alternative household energy source.¹ In developing countries, especially in the rural areas, the use of wood, dung, and crop residues are common resources for cooking and heating, and even in developed countries, are sometimes used for heating. The indoor air pollution derived from burning biomass fuels causes significant global morbidity and mortality, especially in developing countries,²⁻⁴ and has been consistently related to chronic bronchitis, chronic obstructive pulmonary disease (COPD), and acute respiratory infections in children.⁵⁻⁹ Chronic exposure to biomass smoke, including wood smoke, is currently considered to be a risk factor for COPD.⁷⁻⁹

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In rural areas in Colombia, wood is widely used for cooking, especially by women. Due to high migration rates from rural to urban settings over the last few decades, wood smoke COPD (WS-COPD) in women has become more frequent in Colombia's biggest cities.^{5,10} Previous studies have shown clinical, radiographic, and functional differences between WS-COPD and tobacco smoke COPD (TS-COPD). In WS-COPD, the central and peripheral airways are predominantly affected, with minimal or no emphysema defined by CT scan and functional findings.^{11,12}

Bronchial hyperresponsiveness (BHR), a frequent finding in COPD patients, can precede the symptoms and the diagnosis of COPD, and has been related to a more rapid decline in FEV₁.^{13–15} Therefore, BHR is considered by some researchers to be a risk factor for chronic bronchitis and COPD.^{16,17} However, the true importance and physiopathological role of BHR in COPD patients has not been clearly established and it is unknown whether its presence and severity is related to the inflammatory changes of the airways.¹⁸ The aim of this study is to describe BHR in women with WS-COPD and establish a comparison with TS-COPD.

Material and methods

Patients

This is a cross-sectional study. Therefore, the sample was established from consecutive ambulatory patients of the COPD Program of the Fundacion Neumologica Colombiana (Bogotá, Colombia), with the following inclusion criteria: (1) women older than 40 years; (2) COPD diagnosis based on symptoms, FEV₁/FVC < 70%, FEV₁ < 80% of the predicted value, and pre–post bronchodilator change of FEV₁ ≤ 12% and 200 mL; (3) history of significant exposure to tobacco smoke (>20 packs/year) or wood smoke (>20 years); (4) clinical stability in the last six weeks defined as no changes in treatment and no acute exacerbations. Exclusion criteria included history of exposure to both risk factors (tobacco and wood smoke); less than one year of exposure cessation; contraindications for methacholine challenge test (MCT); a particularly severe airflow obstruction (FEV₁ < 50%); and respiratory disease other than COPD, especially asthma (medical diagnosis or high probability: recurrent episodes of wheezing starting before 40 years old) and allergic rhinitis. The patients were divided into two groups: (1) WS-COPD, wood smoke-exposed (no exposure to tobacco smoke); and (2) TS-COPD, tobacco smoke-exposed (no exposure to wood smoke). The study was approved by the Institutional Ethics Committee and all participants signed informed consent forms.

Measurements

Spirometry

A V-MAX 20C (Sensormedics®, Yorba Linda, CA) was used to perform the flow-volume curves and to measure the inspiratory capacity (IC) at baseline and after each methacholine concentration using the ATS (American Thoracic Society)/European Respiratory Society standardized methods¹⁹ and the Crapo's reference values.²⁰ Patients were instructed and trained to perform the IC maneuvers. IC was selected as the highest value from three acceptable maneuvers done at baseline and after each stage of the MCT. The FEV_{25–75}/FVC quotient was calculated for each patient.

BHR measurement

BHR was evaluated using a MCT that was performed according ATS criteria.²¹ Any drug that could affect the MCT results was withdrawn. A five-breath dosimeter protocol was used with progressive concentrations of methacholine (Provocholine® Methapharm, Inc): 0.0625 mg/mL, 0.25 mg/mL, 1 mg/mL, 4 mg/mL, and 16 mg/mL. The best FEV₁ and IC data from the acceptable and repeatable maneuvers were registered. The test ended when the FEV₁ fell ≥20% from baseline or the five-stage protocol was completed. At the end of the test, all patients received salbutamol 400 µg using a dose-metered pressurized inhaler with a space chamber. The presence of cough, phlegm, and wheezing, as well as the respiratory rate, heart rate, and the pulse oxymetry (SpO₂) were registered at each stage of the test. Dyspnea during usual daily activities was evaluated immediately before the MCT using the five-stage Medical Research Council scale²² and during the MCT using the Borg Scale.²³

BHR interpretation

The severity of BHR was established according to the methacholine concentration (mg/mL), which produced a 20% fall in the FEV₁ (PC₂₀) as follows: normal response, PC₂₀ > 16; borderline BHR, PC₂₀ 4.0–16; mild BHR, PC₂₀ 1–4.0; and, moderate to severe BHR, PC₂₀ < 1.0.²¹

Statistical analysis

Mean and standard deviation for continuous variables and proportions for categorical variables were determined using SPSS statistics software (version 10.0; SPSS, Chicago, IL). The geometric mean of PC₂₀ was calculated for each group (WS-COPD and TS-COPD). The differences were estimated using the Student's *t*-test for continuous variables with normal distribution and the Mann–Whitney U test for non-normal variables. The chi-square test or the Fisher's exact

test were used for the categorical variables when the expected frequency was smaller than five. Univariate correlation between age and PC_{20} was also calculated. A two-tailed hypothesis was stated with a significance level of <0.05 (P -value).

Results

Baseline characteristics

Thirty-one women with COPD were included in this study, 19 with WS-COPD and 12 with TS-COPD. The WS-COPD group reported 42 ± 15 years of exposure to wood smoke, and the TS-COPD group reported 43 ± 13 packs/year of smoking. There were no significant differences in age, body mass index, inspiratory capacity, or spirometry values at baseline (Table 1). Furthermore, there were no significant differences in the COPD medications such as inhaled salbutamol (WS-COPD: 50% versus TS-COPD: 42%, $P = 0.47$), inhaled ipratropium bromide (67% versus 67%, $P = 1.00$), inhaled steroids (33% versus 42%, $P = 0.42$), and theophylline (22% versus 8%, $P = 0.62$).

Metacholine challenge testing

Both WS-COPD and TS-COPD patients had a positive result for the MCT ($PC_{20} < 16$ mg/mL). The fall in the FEV_1 and the IC at the end of the test was similar in both groups (Table 2, Figure 1). The BHR level was significantly higher in the WS-COPD group than in the TS-COPD group (0.39 versus 1.24 mg/mL, $P = 0.028$). The majority of the WS-COPD patients had moderate to severe BHR ($PC_{20} < 1$ mg/mL) compared to the TS-COPD patients who were similarly distributed in moderate to severe and in mild BHR (PC_{20} 1–4.0 mg/mL) (Figure 2). After the administration

of salbutamol, the FEV_1 and IC similarly returned to the baseline value in both groups. There was no correlation between age and PC_{20} ($r^2 = 0.34$, $P = 0.324$).

Symptoms and signs

There were no differences between the WS-COPD and TS-COPD groups in terms of chronic dyspnea, which was measured by the Medical Research Council scale (Table 1), at the end of the methacholine challenge test according to the Borg Scale (Table 2), neither in cough (WS-COPD: 77.8% versus TS-COPD: 63.6%, $P = 0.34$) nor phlegm (WS-COPD: 22.2% versus TS-COPD: 36.4%, $P = 0.34$). All the patients showed a significant increase in their respiratory rate, but no significant changes were observed in the heart rate or pulse oximetry (Table 2). Although wheezing was found more frequently in the WS-COPD patients (WS-COPD: 44% versus TS-COPD: 27%), the difference was not statistically significant ($P = 0.30$).

Discussion

This study found that patients with COPD related to wood smoke have more severe BHR than patients with COPD related to tobacco smoke with similar levels of baseline airflow obstruction, age, duration of smoke exposure, respiratory symptoms, and current medication use. All patients had BHR, but among the WS-COPD patients, the BHR was more frequently moderate to severe, while half of the TS-COPD patients had mild hyperresponsiveness.

BHR is related to age, sex, respiratory symptoms, airway size (diameter), baseline lung function, lung size, airway size disproportion, and treatment. Previous studies have found an increase in the prevalence of BHR in older adults.²⁴ However,

Table 1 Baseline characteristics of patients

	WS-COPD (n = 19)	TS-COPD (n = 12)	P
Age (years)	72.7 ± 7.3	66.5 ± 10.3	0.06
BMI (kg/m ²)	27.3 ± 4.3	28.3 ± 4.0	0.50
Wood smoke exposure, years	42 ± 15	NE	–
Tobacco smoke, pack/year	NE	43 ± 13	–
FVC (% predicted)	90.1 ± 13.9	84.2 ± 13.6	0.26
FEV_1 (% predicted)	65.5 ± 11.1	64.2 ± 10.5	0.74
FEV_1/FVC	56.9 ± 8.2	60.4 ± 6.6	0.22
FEF_{25-75} (% predicted)	29.6 ± 10.1	29.5 ± 6.8	0.97
FEF_{25-75}/FVC	0.26 ± 0.08	0.29 ± 0.07	0.35
IC (% predicted)	79.7 ± 15.0	88.6 ± 18.9	0.16
Dyspnea (MRC scale)	2.1 ± 1.1	2.2 ± 1.3	0.80

Note: Values are presented as mean ± SD.

Abbreviations: COPD, chronic obstructive pulmonary disease; WS-COPD, wood smoke COPD; TS-COPD, tobacco smoke COPD; BMI, body mass index; FVC, forced vital capacity; FEV_1 , forced expiratory volume in the first second; FEF_{25-75} , forced expiratory flow at 25%–75% of FVC; IC, inspiratory capacity; NE, no exposure; SD, standard deviation; MRC, Medical Research Council.

Table 2 Characteristics at the end of the methacholine challenge test

	WS-COPD (n = 19)	TS-COPD (n = 12)	P
FEV ₁ (% predicted)	46.6 ± 9.8	47.0 ± 9.3	0.91
FEV ₁ decrease (%)	-29.3 ± 7.6	-27.0 ± 5.0	0.36
IC (% predicted)	56.5 ± 10.2	60.0 ± 17.1	0.54
IC decrease (%)	-27.2 ± 13.7	-32.4 ± 12.4	0.30
Heart rate change (beat/min)	2.5 ± 5.0	4.2 ± 5.5	0.40
Respiratory rate change (breath/min)	6.5 ± 3.4	6.0 ± 2.1	0.62
SpO ₂ change (%)	-0.8 ± 2.1	-0.1 ± 1.9	0.31
Dyspnea (Borg Scale)	1.9 ± 1.5	2.2 ± 2.0	0.61

Note: Values are presented as mean ± SD.

Abbreviations: COPD, chronic obstructive pulmonary disease; WS-COPD, wood smoke COPD; TS-COPD, tobacco smoke COPD; FEV₁, forced expiratory volume in the first second; IC, inspiratory capacity; SD, standard deviation; SpO₂, pulse oximetry.

in this study, the age of the WS-COPD and the TS-COPD patients was similar, and an additional analysis found no correlation between age and PC₂₀. Because women have higher BHR and experience more negative impacts from smoking tobacco than men,²⁵⁻²⁷ this study only included women as subjects in order to avoid the possible effect of gender. BHR is also linked to airflow obstruction severity, expressed by FEV₁, and the disproportion between airway diameter and lung volume, which is indirectly estimated by FEF₂₅₋₇₅/FVC – the lower the FEV₁ and FEF₂₅₋₇₅/FVC, the higher the BHR.^{28,29} In this study, the FEV₁ and the FEF₂₅₋₇₅/FVC were similar in both groups. The IC, which is a useful measurement of dynamic hyperinflation during spontaneous and methacholine-induced acute bronchoconstriction in asthmatic patients,³⁰ was also similar at baseline and after the MCT for both groups. During the methacholine test, no

differences were observed between the two groups in terms of respiratory symptoms such as changes in cough, phlegm, or dyspnea. Similarly, no significant differences in the recent stable treatment were found. Finally, according to the ATS criteria, the appropriate drugs were withdrawn before the methacholine challenge test.

Therefore, none of the mentioned factors associated with BHR could explain the higher severity of BHR in the WS-COPD group, which suggests that other factors, likely related to different characteristics of the disease in these two groups, could be involved. In previous studies, we have described significant differences between WS-COPD and TS-COPD patients. In an initial study, comparing 86 WS-COPD patients with 53 TS-COPD patients, we found that women with WS-COPD had a less severe decrease in carbon monoxide diffusing capacity (DL_{CO}) when compared

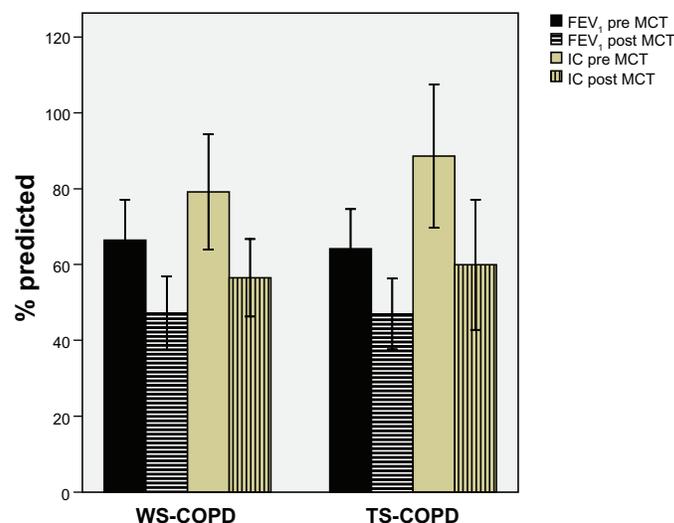


Figure 1 Decline in FEV₁ and IC (% predicted) after the methacholine challenge test for WS-COPD and TS-COPD groups.

Note: Error bars ± 1 SD.

Abbreviations: COPD, chronic obstructive pulmonary disease; WS-COPD, wood smoke COPD; TS-COPD, tobacco smoke COPD; FEV₁, forced expiratory volume in the first second; IC, inspiratory capacity; MCT, methacholine challenge test; SD, standard deviation.

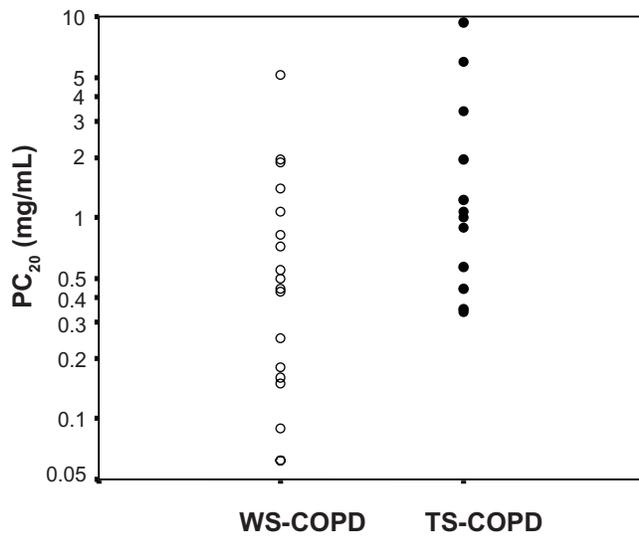


Figure 2 BHR severity according to PC_{20} for each patient. **Notes:** Open circles (○) represent WS-COPD, filled circles (●) represent TS-COPD. Geometric mean of PC_{20} : WS-COPD versus TS-COPD: 0.39 (0.06–5.13) versus 1.24 (0.34–9.39), $P = 0.028$. **Abbreviations:** COPD, chronic obstructive pulmonary disease; WS-COPD, wood smoke COPD; TS-COPD, tobacco smoke COPD; BHR, bronchial hyperresponsiveness; PC_{20} , provocative concentration causing a 20% fall in FEV_1 .

to women with TS-COPD with a nearly normal transfer coefficient (DL_{CO}/VA).¹¹ This functional pattern suggests a predominance of small airway disease in WS-COPD patients, similar to what has been described in patients with airflow obstruction, compromise of peripheral small airways, and mild or no emphysema.^{31,32} This hypothesis was confirmed in a further study that used a qualitative evaluation of high-resolution CT scan and found that WS-COPD women frequently had sub-segmentary atelectasis, severe thickening of the bronchial walls, bronchiectasis, and mild or no emphysema in comparison with TS-COPD patients who showed a significantly higher index of emphysema with mild changes in airways.¹² These functional and tomographic findings can be correlated with those observed in a retrospective study of 103 autopsies of subjects exposed to wood smoke in which the main findings were hypertensive changes of the pulmonary vessels, peribronchial, perivascular, and interstitial depositions of anthracotic pigment, and the absence of emphysema.³³ The descriptions of the bronchoscopic abnormalities found in women exposed to wood smoke include mucosal hyperemia and edema, irregular reduction of the lumen, and in some cases, severe anthracotic plaques.³⁴

Based on the results of this study and previous observations, we speculate that the higher BHR observed in WS-COPD patients could be related to differences in

the structure and inflammatory response of their airways, compared to TS-COPD patients. The relationship between BHR and airway inflammation in patients with COPD related to tobacco smoke has not been clearly defined.³⁵ In some studies, the correlation between inflammatory markers like exhaled nitric oxide or sputum eosinophils and the PC_{20} has been weak, but others have shown that the more severe the airway inflammation, the higher the rate of BHR.^{36,37} In addition, no functional indexes evaluating the lung parenchyma structure like pressure-volume curves or diffusion capacity (DL_{CO}) have been related to BHR, which suggests that BHR is more closely related to airway abnormalities (inflammation and lumen reduction) in COPD patients.³⁸ However, no differences have been observed between BHR in patients with chronic bronchitis and those with emphysema.³⁹

BHR is considered a risk factor for COPD as it may precede its symptoms, and is associated with the early decline of lung functions in healthy young adults, accelerated impairment of airflow obstruction in COPD patients, and higher mortality.^{13,15,17} The cross-sectional design of this study does not allow us to conclude that BHR is a risk factor for COPD related to wood smoke, but the finding of more severe BHR in WS-COPD than in TS-COPD patients suggests that it may play a role in the physiopathology of WS-COPD that is possibly related to airway inflammation.

Some limitations of this study include the relatively small number of patients and the absence of other measurements of airway inflammation such as bronchial biopsies or cellular and biochemical sputum examinations. However, the rigorous selection of the patients according to exposures favored the conformation of very different groups and a reliable comparison. Because WS-COPD is more frequent in women, we excluded males; therefore, the results of this study cannot be generalized to men with COPD.

Conclusion

This study found the occurrence of moderate to severe BHR in women with WS-COPD that was more severe than in TS-COPD women with similar age and airflow obstruction. We speculate that the structural and inflammatory changes induced by the chronic exposure to wood smoke, described in other studies, explains the BHR severity in WS-COPD patients and the differences when compared to TS-COPD patients. Future studies may clarify our understanding of the

impact of BHR on COPD physiopathology, phenotypes, and treatment strategies.

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Disclosure

The authors report no conflicts of interest in this work.

References

- World Resources Institute UNEP UNDP World Bank. *1998–1999 World Resources: a Guide to the Global Environment*. Oxford: Oxford University Press; 1998.
- Bruce N, Perez-Padilla R, Albalak R. Indoor air pollution in developing countries: a major environmental and public health challenge. *Bull World Health Organ*. 2000;78:1078–1092.
- Smith KR. National burden of disease in India from indoor air pollution. *Proc Natl Acad Sci U S A*. 2000;97:13286–13293.
- Ezzati M, Kammen DM. The health impacts of exposure to indoor air pollution from solid fuels in developing countries: knowledge, gaps, and data needs. *Environ Health Perspect*. 2002;110:1057–1068.
- Dennis RJ, Maldonado D, Norman S, Baena E, Martinez G. Woodsmoke exposure and risk for obstructive airways disease among women. *Chest*. 1996;109:115–119.
- Perez-Padilla R, Regalado J, Vedal S, et al. Exposure to biomass smoke and chronic airway disease in Mexican women. A case-control study. *Am J Respir Crit Care Med*. 1996;154:701–706.
- Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med*. 2001;163:1256–1276.
- Torres-Duque C, Maldonado D, Perez-Padilla R, Ezzati M, Viegi G; on behalf of the Forum of International Respiratory Societies (FIRS) Task Force on Health Effects of Biomass Exposure. Biomass fuels and respiratory diseases: a review of the evidence. *Proc Am Thorac Soc*. 2008;5:577–590.
- Hu G, Zhou Y, Tian J, et al. Risk of chronic obstructive pulmonary disease from exposure to biomass smoke: a meta-analysis. *Chest*. 2010;138:20–31.
- Caballero A, Torres-Duque CA, Jaramillo C, et al. Prevalence of COPD in Five Colombian Cities Situated at Low, Medium, and High Altitude (PREPOCOL Study). *Chest*. 2008;133:343–349.
- González M, Páez S, Jaramillo C, Barrero M, Maldonado D. Enfermedad pulmonar obstructiva crónica (EPOC) por humo de leña en mujeres. [Chronic obstructive pulmonary disease (COPD) produced by wood smoke in women]. *Acta Med Colomb*. 2004;29:17–25. Spanish.
- González M, Maldonado D, Pérez J, Varón H. Pseudoenfisema en mujeres con EPOC por humo de leña en Bogotá (2600 m) [Pseudophysiologic emphysema in women with wood smoke COPD in Bogotá (2600 m)]. *Arch Bronconeumol*. 2004;40:31. Spanish.
- Tashkin DP, Altose MD, Connett JE, Kanner RE, Lee WW, Wise RA. Methacholine reactivity predicts changes in lung function over time in smokers with early chronic obstructive pulmonary disease. The Lung Health Study Research Group. *Am J Respir Crit Care Med*. 1996;153:1802–1811.
- Xu X, Rijcken B, Schouten JP, Weiss ST. Airways responsiveness and development and remission of chronic respiratory symptoms in adults. *Lancet*. 1997;350:1431–1434.
- Hospers JJ, Postma DS, Rijcken B, Weiss ST, Schouten JP. Histamine airway hyper-responsiveness and mortality from chronic obstructive pulmonary disease: a cohort study. *Lancet*. 2000;356:1313–1317.
- Vestbo J, Prescott E. Update on the “Dutch hypothesis” for chronic respiratory disease. *Thorax*. 1998;53 Suppl 2:S15–S19.
- Postma DS, Boezen HM. Rationale for the Dutch hypothesis. Allergy and airway hyperresponsiveness as genetic factors and their interaction with environment in the development of asthma and COPD. *Chest*. 2004;126 Suppl 2:96S–104S.
- van den BM, Polosa R, Kerstjens HA, Postma DS. The role of endogenous and exogenous AMP in asthma and chronic obstructive pulmonary disease. *J Allergy Clin Immunol*. 2004;114:737–746.
- Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26:319–338.
- Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis*. 1981;123:659–664.
- Crapo RO, Casaburi R, Coates AL, et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med*. 2000;161:309–329.
- Surveillance for respiratory hazards in the occupational setting [American Thoracic Society]. *Am Rev Respir Dis*. 1982;126:952–956.
- Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc*. 1982;14:377–381.
- Scichilone N, Messina M, Battaglia S, Catalano F, Bellia V. Airway hyperresponsiveness in the elderly: prevalence and clinical implications. *Eur Respir J*. 2005;25:364–375.
- Kanner RE, Connett JE, Altose MD, et al. Gender difference in airway hyperresponsiveness in smokers with mild COPD. The Lung Health Study. *Am J Respir Crit Care Med*. 1994;150:956–961.
- 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;10:822–827.
- Langhammer A, Johnsen R, Gulsvik A, Holmen TL, Bjermer L. Sex differences in lung vulnerability to tobacco smoking. *Eur Respir J*. 2003;21:1017–1023.
- Litonjua AA, Sparrow D, Weiss ST. The FEF25-75/FVC ratio is associated with methacholine airway responsiveness. The normative aging study. *Am J Respir Crit Care Med*. 1999;159:1574–1579.
- Urrutia I, Capelastegui A, Quintana JM, et al. Association between the forced midexpiratory flow/forced vital capacity ratio and bronchial hyperresponsiveness. *Arch Bronconeumol*. 2004;40:397–402. Spanish.
- Tantucci C, Ellaffi M, Duguet A, et al. Dynamic hyperinflation and flow limitation during methacholine-induced bronchoconstriction in asthma. *Eur Respir J*. 1999;14:295–301.
- Gelb AF, Hogg JC, Muller NL, et al. Contribution of emphysema and small airways in COPD. *Chest*. 1996;109:353–359.
- Gelb AF, Zamel N, Hogg JC, Muller NL, Schein MJ. Pseudophysiologic emphysema resulting from severe small-airways disease. *Am J Respir Crit Care Med*. 1998;158:815–819.
- Palacios D, Mendez O. Neumopatía por humo de leña. Un estudio en autopsias [Pneumopathy due to inhaling firewood smoke. Autopsy findings from the San Juan de Dios Hospital]. *Biomédica*. 1998;18:153–160. Spanish.
- Restrepo J, Reyes P, de Ochoa P, Patiño E. Neumoconiosis por inhalación de humo de leña [Pneumoconiosis due to inhalation of wood smoke]. *Acta Med Colomb*. 1983;8:191–204. Spanish.
- Postma DS, Kerstjens HA. Characteristics of airway hyperresponsiveness in asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1998;158:S187–S192.
- Lapperre TS, Snoeck-Stroband JB, Gosman MM, et al. Dissociation of lung function and airway inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2004;170:499–504.

37. Mullen JB, Wiggs BR, Wright JL, Hogg JC, Pare PD. Nonspecific airway reactivity in cigarette smokers. Relationship to airway pathology and baseline lung function. *Am Rev Respir Dis.* 1986;133:120–125.
38. Verhoeven GT, Verbraak AF, Boere-van der Straat S, Hoogsteden HC, Bogaard JM. Influence of lung parenchymal destruction on the different indexes of the methacholine dose-response curve in COPD patients. *Chest.* 2000;117:984–990.
39. Verma VK, Cockcroft DW, Dosman JA. Airway responsiveness to inhaled histamine in chronic obstructive airways disease. Chronic bronchitis vs emphysema. *Chest.* 1988;94:457–461.

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