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Smoke, biomass exposure and COPD risk in the primary care setting: the PUMA study

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Author contributions

All authors contributed to the study concept, design, acquisition of data, analysis and interpretation of data. MMO took the lead role in drafting of the manuscript while all authors provided critical revision of the manuscript, read and approved the final version and agreed to its submission for publication.

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Conflicts of Interest

Filip Surmont is an employee of AstraZeneca Latin America.

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Abstract

Background: The evidence indicates that other risk factors different to smoking are important in the development of COPD. It has been postulated that less traditional risk factors (example exposure to coal and/or biomass smoke) may interact with smoking to further increase the COPD risk. This analysis evaluated the exposure to biomass and smoking on COPD risk in a primary care setting from Latin America.

Methods: Subjects attending routine primary care visits, ≥40 years, current or former smokers or exposed to biomass smoke, completed a questionnaire and performed spirometry. COPD was defined as post-bronchodilator (post-BD) forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) <0.70 and the lower limit of normal (LLN). Smoking was defined by pack-years (≤20, 20–30, >30) and biomass exposure as an exposure to coal or wood (for heating, cooking, or both) for ≥10 years.

Results: 1743 individuals completed the questionnaire, and 1540 performed spirometry. Irrespective of COPD definition, approximately 40% of COPD subjects reported exposure to biomass versus 30% of those without COPD. A higher proportion of COPD patients (post-BD FEV_1/FVC<0.70) than those without COPD smoked >30 pack-years (66% vs 39%); similar results were found with LLN definition. Analysis of exposure to biomass >10 years plus smoking >20 pack-years (reference no exposure) found tobacco smoking (crude odds ratio [OR] 4.50, 95%CI 2.73–7.41; adjusted OR 3.30, 95%CI 1.93–5.63) and biomass exposure (crude OR 3.66, 95%CI 2.00–6.73; adjusted OR 2.28, 95%CI 1.18–4.41) were risk factors for COPD, with smoking a possible

confounder for the association between biomass and COPD (post-BD FEV_1/FVC<0.70); similar results were found with LLN definition.

Conclusion: COPD subjects from primary care had a higher exposure to biomass and smoking compared with non-COPD. Smoking and biomass are both risk factors for COPD, but they do not appear to have an additive effect.

Word count: 300 words (max: 300 words)

Key words: COPD, smoke, biomass exposure, primary care.

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease of high prevalence, morbidity and mortality worldwide, and is associated with exposure to toxic particles and smoke.[1–9] Although smoking (tobacco consumption) is widely recognised as the most important risk factor for COPD, it is now also recognised that a substantial proportion of COPD cases (one-quarter to one-third of all cases) cannot be explained only by smoking, and the disease also occurs in non-smokers. A statement by the American Thoracic Society (ATS) on novel risk factors and the global burden of COPD reported that the population-attributable fraction (PAF) for smoking as a cause of COPD was less than 80% of those involved most clinical studies, indicating that other risk factors in addition to cigarette smoking are important in the development of the disease.[10]

The Latin American Project for the Investigation of Lung Disease (PLATINO) population-based study showed that among 5,315 subjects studied, 2278 had never smoked and 3036 were current or ex-smokers. COPD was observed in 3.5% of those who had never smoked and in 7.5% of those that had smoked.[11] The prevalence of COPD in those who have never smoked has also been reported in other population-based studies.[12–15]

The results of these population-based studies suggest that predictors of COPD in those that have never smoked include older age, female gender, a prior diagnosis of asthma or tuberculosis, lower education level, increased body mass index (BMI), exposure to environmental tobacco smoke, coal and/or biomass smoke, poor ventilation in the kitchen, a family history of respiratory disease and childhood respiratory diseases.[11–13] In the other hand, it has been

suggested that some of these less traditional COPD risk factors in particular biomass exposure, may interact with smoking to further increase the risk of COPD. Moreover, Lopez-Campos et al showed that those patients with COPD who were exposed to both tobacco and biomass smoke had increased oxygen usage and decreased quality of life.[16]

There is a relative lack of information from the primary care setting regarding the history of smoking and biomass exposure in COPD and non-COPD subjects, as well as on the possible additive effect among these exposures to increase the risk of COPD. Recently, the **P**revalence St**U**dy and Regular Practice, Diagnosis and Treat**M**ent Among General Practitioners in Populations at Risk of COPD in Latin **A**merica (PUMA) study, conducted in primary care setting, evaluated the prevalence of airflow limitation in a population at risk for COPD.[17,18] This study offered a good opportunity to assess different aspects of the disease in a large international primary care sample from Latin America. Therefore, the aims of the present study were to: 1) describe the history of smoking and biomass exposure in this primary care population; 2) analyse the exposure to biomass and smoking in COPD (using different spirometric definitions) and non-COPD subjects; and 3) measure the association between biomass exposure and tobacco smoking (pack-years) and COPD (using different spirometric definitions).

Methods

PUMA was conducted in the primary care setting of four Latin American countries: Argentina, Colombia, Venezuela and Uruguay. Complete methodology has been published elsewhere.[17–20] Briefly, this was a multicentre, multinational, cross-sectional, non-interventional study including primary care centres without direct connection with respiratory medicine specialists that were selected to reflect national primary care practice in terms of geographical distribution and healthcare sector. Patients were recruited during routine spontaneous or scheduled medical appointment unrelated to the study (with or without symptoms). The study was approved by the ethics committees for each site. All patients provided written informed consent.

At-risk patients were included if they were ≥40 years of age, current or ex-smokers (≥10 pack-years, ≥50 pipes/year, or ≥50 cigars/year), and/or exposed to biomass smoke (wood or coal, for cooking or heating; exposure ≥100 h/year).

Participants completed a modified version of the PLATINO study questionnaire[1] for information on factors potentially associated with COPD; these included demographics, smoking habits, biomass exposure, education, employment, respiratory symptoms, use of respiratory medication and prior spirometric testing. Data on prior medical diagnosis of tuberculosis, asthma, chronic bronchitis, emphysema, COPD, self-reported exacerbations and hospitalisations were also obtained. Spirometry was performed using the portable, battery-operated ultrasound Easy One spirometer (ndd Medical Technologies, Zurich, Switzerland). Spirometry tests were performed at

baseline and 15 min after the administration of 400 µg salbutamol, according to the American Thoracic Society criteria of acceptability and reproducibility.

The definition of COPD proposed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) was used: post-bronchodilator (post-BD) forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) <0.70.[21] The post-bronchodilator lower limit of normal (LLN) for FEV_1/FVC criteria was also used.

Smoking was defined by pack-years (≤20, 20–30, >30) and biomass exposure as the history of exposure to coal or wood (for heating, cooking or both) at least for 10 years.

Statistical analysis

We performed descriptive analysis using relative frequencies for the variables and comparison of the groups with and without COPD using a chi-square test for heterogeneity. Also, the mean duration of tobacco exposure (smoked pack-years) and of biomass exposure in life were obtained.

For the crude and adjusted models, we used a logistic regression analysis to determine odds ratios (ORs) and the respective 95% confidence intervals (CIs). For the adjusted model, we used as confounders the following variables: sex (male/female), age (complete years), skin colour (white/non-white), schooling (complete years of formal education), BMI (kg/m²), modified Medical Research Council (mMRC) scale, cough (yes/no) and phlegm (yes/no). For the analysis of a possible association of tobacco smoking plus biomass with COPD, these measures were mutually adjusted. All analyses were performed using Stata software (StataCorp. 2013. Stata Statistical Software: Release 13.

College Station, TX: StataCorp LP). P-values less than 0.05 were considered statistically significant.

Results

Participation rates in the PUMA study have been published previously.[17–20] Among the 1743 subjects that completed interviews, 1540 had acceptable spirometry. Based on post-BD FEV_1/FVC <0.70 criteria, COPD was present in 309 subjects, and was present in 226 subjects using LLN criteria.

Baseline demographics and characteristics of subjects with or without COPD in the PUMA population, according to post-BD FEV_1/FVC <0.70 and LLN criteria, are shown in **Table 1**. As expected, subjects with COPD (defined using either criteria) were older, predominantly male, had a lower BMI (below 25 kg/m^2), reported more respiratory symptoms (dyspnoea, cough and phlegm), self-reported asthma and had a mMRC scale ≥2 compared with those without COPD.

Exposure to biomass for >10 years and to tobacco smoke for ≥10 pack-years in COPD subjects according to post-BD FEV_1/FVC <0.70 criteria and LLN criteria are shown in **Figures 1 and 2**, respectively. Irrespective of COPD definition used, a greater proportion of subjects with COPD (approximately 40%) reported exposure to biomass in comparison with subjects without COPD (approximately 30%) (**Figure 1**). A greater proportion of subjects with COPD, defined by post-BD FEV_1/FVC <0.70, compared with subjects without COPD smoked more than 30 pack-years (66% vs 39%); similar results were found for COPD according to the LLN criteria (**Figure 2**).

The mean number of pack-years smoked during life and the mean years of biomass exposure in subjects with COPD, using either definition of COPD, was higher than in those with COPD than those without the disease (**Figure 3**).

COPD patients, for both definitions, had an average of 44 pack-years of tobacco smoking and 12 years of biomass exposure (**Figure 3**).

The association between biomass exposure and tobacco smoking (pack-years smoked) with COPD in shown in **Table 2**. Biomass exposure (>10 years) was found to be a risk factor for COPD (defined using both criteria) in the crude analysis, with the risk of COPD increasing with increased exposure (**Table 2**); however, this did not reach statistical significance in the adjusted analysis (subjects who were exposed to biomass could be also smokers, therefore they could be exposed to both biomass and smoke). The lack of statistical significance in the adjusted analysis could be due to the concomitant presence of smoking. Smoking >20 pack-years was found to be a risk factor for COPD (defined using both criteria) in both the crude and adjusted analysis, with increased smoking further increasing the risk of COPD (**Table 2**). In the analysis of exposure to both biomass and/or smoking, it would appear that while both tobacco smoking and biomass exposure are risk factors for COPD (unique effect of those only exposed to biomass or to smoking are significant), the adjusted OR might suggest that smoking is a possible confounding factor for the association between biomass and COPD (**Table 2**).

Discussion

The main findings of this study on tobacco smoke, biomass exposure and COPD risk in a primary care setting were: first, a higher proportion of patients with COPD reported exposure to biomass and tobacco smoke compared with those without COPD, and the most frequent source of biomass exposure was cooking; second, increased tobacco smoking and biomass exposure further increased the risk of COPD, but smoking appeared to be a confounding factor for the association of biomass and COPD.

The major effects of smoking in COPD have been extensively documented for many years. Several population-based studies in primary care setting have reported the smoking pattern in subjects with and without COPD.[22–24] In the PLATINO study; tobacco smoking was higher in COPD subjects compared with those without COPD (19.4 vs. 9.1 pack-years). The proportion of current smokers and ex-smoker were also higher in those with COPD than in those without the disease (current smokers: 36.0% vs 28.8%; ex-smokers: 32.5% vs 26.8%).[22] In addition, both females and males with COPD reported higher tobacco smoking compared with persons without COPD (females: 11.6 vs 6.0 pack-years; males: 26.5 vs 14.1 pack-years).[23] Data from a primary care study of subjects at least 45 years of age and with a history of smoking showed that subjects with COPD have higher smoking index than those without COPD (52.6 vs 32.1 pack-years).[24] The results of the present analysis indicate that a larger proportion of subjects with COPD than those without COPD smoked more than 30 pack-years (66% vs 39%). The proportion of subjects that smoked ≤20 pack-years was only 18% in the group with COPD (defined as post-BD FEV_1/FVC <0.70) and 37.5% in those without the disease.

Our results, therefore, are consistent with previous reports and argue in favour of smoking as a strong risk factor for COPD, with higher COPD risk with increased smoking even though this population already has a moderate to high tobacco use.

Although cross-sectional and cohort studies have consistently shown that smoking is one of the most important risk factors for COPD, a wide variation in the population-attributable fraction (PAF) for smoking as a cause of COPD has been reported (ranging from 9.7 to 97.9%).[10] The evidence indicates that a substantial proportion of COPD cases cannot be attributed to smoking and that other risk factor are important in the development of COPD.[11–13,25,26] In the PLATINO study, age, current smoking, indoor exposure to coal and exposure to dust in the workplace were the risk factors presenting the highest aetiological fractions for COPD.[1] Attributable risk for COPD was 52% for being 60 years of age or older, and for modifiable risk factors the risk was 27% for being a current smoker, 11% for exposure to coal for ≥10 years and 9% for exposure to dust in the workplace for ≥10 years. Other factors, including male, poor education, exposure to biomass, history of tuberculosis, low BMI and childhood admission due to respiratory problems, presented an attributable risk below 10%.[1]

A sub-analysis of the BOLD program assessed the risk factors for COPD and they found significant associations between COPD and smoking, environmental tobacco exposure, age, education, tuberculosis, hospitalisation for respiratory illness below the age of 10 years, a family history of COPD and working in dusty jobs.[26] Additional evidence for the contribution of other risk factors besides smoking results from the occurrence of COPD in those that

have never smoked, with a prevalence ranging from 3 to 15% in different populations.[12,13,25,27] The PLATINO study reported a COPD prevalence of 3.5% and 7.5% in those that had never smoked and current/ex-smokers, respectively.[11] Terzikhan et al found that COPD prevalence was 17.8% in smokers and 6.4% in non-smokers.[25] The overall prevalence of COPD among non-smokers in a large Chinese population-base study was 5.2%,[12] and 6.4% in a Canadian study (representing 27% of all COPD subjects).[27] Using GOLD criteria to define COPD, the BOLD study reported an overall prevalence of 5.2% in those that had never smoked, which represented 27.7% (523/1,889) of all COPD cases.[13] They identified that female gender, increased age, prior diagnosis of asthma, childhood infections, organic dust and lower education levels were all associated with increased risk for COPD among those that had never smoked.[13]

The relationship between exposure to indoor biomass smoke and the development of COPD continues to be an area of controversy. The results of a meta-analysis showed that persons exposed to biomass smoke have an OR of 2.44 (95% CI: 1.90–3.33) for the development of COPD compared with those unexposed.[28] The study also reported that exposure to tobacco smoke was a risk factor for the development of COPD in both genders, although whether an interaction exists between these risk factors remains unclear.[28] Another meta-analysis established that biomass exposure is associated with risk COPD, but smoking status was not taken into account.[29] In the BOLD study, biomass exposure was not different between those with or without COPD; however, when COPD subjects were grouped by airflow limitation severity, those with moderate to severe COPD reported more frequently a history of biomass

exposure than control subjects.[13] Zhong et al showed that biomass exposure was associated with an increased risk of developing COPD among a Chinese population,[30] and the CanCOLD study showed that the relationship between biomass exposure and COPD remained when the analysis was adjusted for gender.[27]

Our findings are consistent with most of the previous studies in that biomass exposure is a risk factor for developing COPD. Moreover, a higher proportion of our COPD subjects reported exposure to biomass than those without COPD. A possible explanation for the discrepancies with other studies (BOLD or CanCOLD) could be the result of differences in the population studied (primary care setting vs population-based) and the source of biomass exposure (heating vs indoor cooking).

It has been postulated that some of the less traditional risk factors may interact with smoking to further increase the risk of COPD. However, few studies have compared the two smoke-related risk factors in the same population and even fewer studies have tried to assess the interaction between these two factors for developing COPD. There are some important limitations when explore this relationship, which include the different patterns of smoke exposure and measurement of the magnitude of each exposure. Most exposure estimations cannot predict the dose of contaminant and generally only estimate exposure time.[31,32] The main exception is tobacco smoking as pack-years has been validated for cumulative smoking exposure as a risk factor for many diseases. This level of validation, without air quality measurement (particle pollution) or exposure biomarkers (e.g. CO in exhaled air), are still in development, or lacking, for exposure to other types of smoke (e.g. biomass or

other smoking such as water-pipe or marihuana). Despite this limitation, some reports have explored these relationships.

Sood et al determined whether wood smoke exposure was a risk factor for COPD in a current smoker population and whether aberrant gene promoter methylation in sputum modified this association.[33] Their findings indicate that wood smoke exposure was independently associated with a lower FEV_1, a higher prevalence of airflow obstruction and chronic bronchitis, and these associations were stronger among current tobacco smokers. In addition, smokers that expressed aberrant promoter methylation of the p16 and GATA4 genes in sputum demonstrated stronger associations of wood smoke exposure and lower lung function than those without these epigenetic changes.[33] Another relevant finding in the study was that New Mexican non-Hispanic white persons were at greater risk for wood smoke-associated COPD than Hispanic persons in general. The authors concluded that exposure to wood smoke and gene promoter methylation synergistically increased the risk of reduced lung function in cigarette smokers, which supports an additive effect between current cigarette smoking and wood smoke exposure on some COPD phenotypes.[33] Other authors also reported a significant negative correlation between biomass exposure and lung function, as well as a significant synergistic effect between smoking history and biomass exposure in terms of loss of lung function in a population 18 year of age or older.[34]

In contrast, a case-control Chinese study, showed an increased risk of developing COPD associated with tobacco smoking but not with biomass exposure nor with both risk factors.[35] However, a major limitation was that the

authors did not explain the biomass exposure time estimation or the tobacco index.

Although, our findings showed that tobacco smoking and biomass exposure are risk factors for COPD, they also indicate that smoking seemed to be a confounding factor for biomass. Therefore, it does not allow us to support a possible synergistic or additive effect between these risk factors that further increases the risk of COPD. One possible explanation for this is that the PUMA study evaluated an older population located in major cities in Latin America whereas, for example, da Silva et al studied a younger, rural population[34] while Sood et al evaluated a New Mexican population.[33] Overall, the lack of similar information from other multinational studies in a primary care setting from our region makes it difficult to compare results with the PUMA study.

This study has some limitations that should be highlighted. We acknowledge that the findings from this study cannot be extrapolated to all Latin American countries, as the study was only performed in four countries; this was the result of limited resources within the countries and the availability of centres to participate. Nevertheless, the study procedure used was the most sensible given the operational possibilities in each country. Another limitation is that this was a transversal study and so was only designed to evaluate the characteristics of the patients and there was no follow-up; we did not assess any pathophysiological link for risk factor and COPD that could help explain the findings. The difficulties in measuring exposure to biomass (self-reported history) could be another limitation when measuring the impact of this risk factor in the development of COPD. The associations between exposure to biomass and COPD tend to the nullity due to the way biomass was measured.

Unfortunately, more detailed information on biomass exposure was not collected and further studies need to address this important issue for a better understanding of the real effect of biomass on COPD". Finally, due to the design of the PUMA study, there were no subjects without exposure to risk factors in the study population.

In conclusion, the results of the present study indicate that patients with COPD from primary care in Latin America had a higher exposure to biomass and tobacco smoke in compared with those without the disease. Smoking and biomass exposure are both risk factors for COPD, but they do not seem to have an additive effect on the risk of COPD.

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Figure legends

Figure 1. Exposure to biomass in COPD (defined using post-BD FEV_1/FVC <0.70 and LLN criteria) and non-COPD subjects.

Figure 2. Exposure to pack-years smoked in COPD (defined using post-BD FEV_1/FVC <0.70 and LLN criteria) and non-COPD subjects.

Figure 3. Exposure to biomass (mean years) and pack-year (mean) smoked, in COPD (defined using post-BD FEV_1/FVC <0.70 and LLN criteria) and non-COPD subjects.

Quick look

Current knowledge

COPD is associated with exposure to toxic particles and smoke. Although smoking (tobacco consumption) is widely recognised as the most important risk factor for COPD, it is now also recognised that a substantial proportion of COPD cases cannot be explained only by smoking. It has been suggested that the interaction between some less traditional COPD risk factors, such biomass exposure, with smoking might further increase the risk of COPD. This analysis evaluated the exposure to biomass and smoking on the risk of COPD in a primary care setting in four Latin American countries.

What This Paper Contributes To Our Knowledge

In a primary care setting in four Latin American countries, approximately 40% of COPD subjects reported exposure to biomass versus 30% of those without COPD. A higher proportion of COPD patients than those without COPD smoked >30 pack-years (66% vs 39%). Biomass exposure (>10 years) and tobacco smoking (>20 pack-years) (no exposure as reference) were risk factors for COPD, but they do not appear to have an additive effect.

Table 1. Baseline demographics and characteristics of subjects with and without COPD in the PUMA population, according to post-BD FEV_1/FVC <0.70 and LLN criteria.

	COPD			
	Post-BD FEV_1/FVC <0.70		LLN	
Variable	**No COPD (N=1231)**	**COPD (N=309)**	**No COPD (N=1314)**	**COPD (N=226)**
Sex	*P<0.01*		*P=0.06*	
Female	52.7	44.0	52.0	45.1
Male	47.3	56.0	48.0	54.9
Age (complete years)	*P<0.001*		*P<0.001*	
40–49	23.8	2.2	21.8	5.8
50–59	38.3	23.0	36.9	25.2
60+	37.9	74.8	41.3	69.0
Skin colour	*P=0.66*		*P=0.21*	
White	55.3	53.9	55.7	51.1
Non-white	44.7	46.1	44.3	48.9
Schooling (complete years of formal education)	*P=0.12*		*P=0.14*	
0–8	48.4	53.4	48.6	54.0
9+	51.6	46.6	51.4	46.0
BMI (kg/m²)	*P<0.001*		*P<0.001*	
<25.0	24.8	44.7	25.3	49.1
25.0–29.9	40.4	34.6	40.4	32.7
≥30	34.8	20.7	34.3	18.1
mMRC dyspnoea scale	*P<0.001*		*P<0.001*	
No	58.5	36.4	57.9	32.7
1	19.9	19.9	19.8	20.6
2	10.8	17.8	11.4	16.8
3	9.2	18.2	9.1	21.5
4	1.7	7.7	1.9	8.4
Cough	*P<0.001*		*P<0.001*	
No	70.6	56.3	69.7	56.2
Yes	29.4	43.7	10.3	43.8
Phlegm	*P<0.001*		*P<0.001*	
No	74.0	55.0	72.9	54.4
Yes	26.0	45.0	27.1	45.6
Self-reported asthma	*P<0.001*		*P<0.001*	
No	87.9	73.5	87.2	72.1

Yes	12.1	26.5	12.8	27.9
Self-reported tuberculosis	*P=0.13*		*P=0.57*	
No	98.9	97.7	98.7	98.2
Yes	1.1	2.3	1.3	1.8
Self-reported lung cancer	*P=0.83*		*P=0.84*	
No	99.6	99.7	99.6	99.6
Yes	0.4	0.3	0.4	0.4

BMI: body mass index; mMRC: modified Medical Research Council; Post-BD: post-bronchodilator.

Table 2. Association between biomass exposure and tobacco smoking (pack-years) with COPD (post-BD FEV_1/FVC <0.70 and LLN criteria).

	Post-BD FEV_1/FVC <0.70		LLN	
Variable	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
Biomass (years exposed)	*P<0.001*	*P=0.26*	*P<0.01*	*P=0.62*
0	1.00	1.00	1.00	1.00
>0–10	1.57 (1.10; 2.24)	1.27 (0.84; 1.93)	1.18 (0.78; 1.77)	0.90 (0.56; 1.44)
>10	2.02 (1.50; 2.73)	1.34 (0.92; 1.96)	1.75 (1.26; 2.44)	1.15 (0.76; 1.74)
Biomass (years exposed)	*P<0.001*	*P=0.25*	*P=0.001*	*P=0.57*
0–10	1.00	1.00	1.00	1.00
>10	1.75 (1.33; 2.30)	1.23 (0.87; 1.74)	1.67 (1.23; 2.26)	1.19 (0.81; 1.75)
Pack-years smoked	*P<0.001*	*P<0.001*	*P<0.001*	*P<0.001*
≤20	1.00	1.00	1.00	1.00
>20–30	1.44 (0.94; 2.23)	1.41 (0.87; 2.29)	1.33 (0.82; 2.16)	1.27 (0.75; 2.17)
>30	3.67 (2.62; 5.19)	2.63 (1.80; 3.84)	3.13 (2.15; 4.56)	2.25 (1.48; 3.40)
Pack-years smoked	*P<0.001*	*P<0.001*	*P<0.001*	*P=0.001*
≤20	1.00	1.00	1.00	1.00
>20	2.84 (2.04; 3.95)	2.21 (1.54; 3.18)	2.48 (1.72; 3.57)	1.91 (1.28; 2.85)
Biomass (>10 years) and/or pack-years (>20)	*P<0.001*	*P<0.001*	*P<0.001*	*P=0.006*
No exposure	1.00	1.00	1.00	1.00
Only biomass	**3.66 (2.00; 6.73)**	**2.28 (1.18; 4.41)**	**3.23 (1.66; 6.27)**	**2.14 (1.05; 4.36)**
Only pack-years	**4.50 (2.73; 7.41)**	**3.30 (1.93; 5.63)**	**3.73 (2.16; 6.43)**	**2.80 (1.56; 5.03)**
Both	**6.94 (4.08; 11.80)**	**3.43 (1.87; 6.29)**	**5.50 (3.08; 9.79)**	**2.77 (1.42; 5.39)**

Adjusted analyses were made using sex, age, skin colour, schooling, BMI, self-reported asthma diagnosis, mMRC scale for dyspnoea, cough and phlegm as confounding variables. All analyses were mutually adjusted for smoking and biomass. BMI: body mass index; CI: confide.

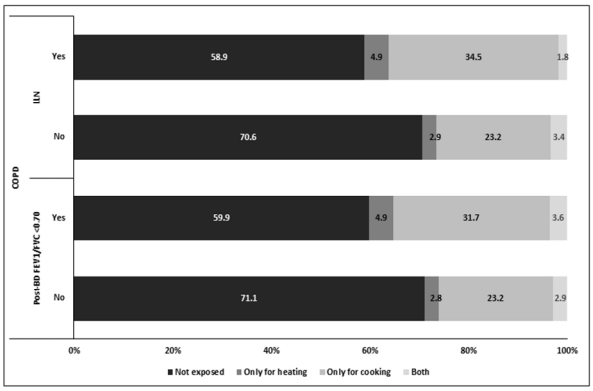

Figure 1. Exposure to biomass in COPD (defined using post-BD FEV1/FVC <0.70 and LLN criteria) and non-COPD subjects.

Figure 1
338x190mm (96 x 96 DPI)

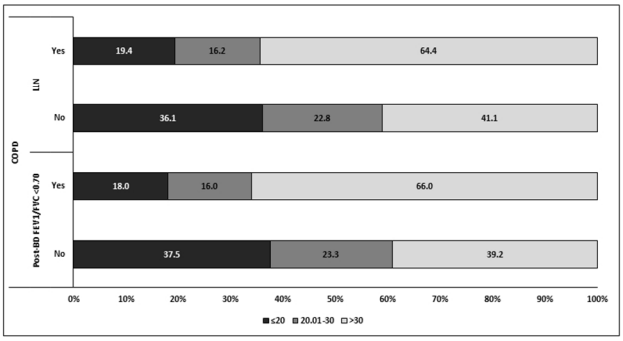

Figure 2. Exposure to pack-years smoked in COPD (defined using post-BD FEV1/FVC <0.70 and LLN criteria) and non-COPD subjects.
Figure 2
338x190mm (96 x 96 DPI)

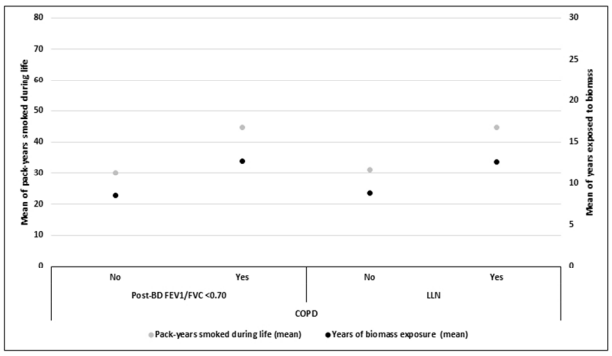

Figure 3. Exposure to biomass (mean years) and pack-year (mean) smoked, in COPD (defined using post-BD FEV1/FVC <0.70 and LLN criteria) and non-COPD subjects.
Figure 3
338x190mm (96 x 96 DPI)