



# Tuberculosis and tobacco: is there any epidemiological association?

*To the Editor:*

Tobacco smoking has been suspected to be a risk factor for tuberculosis (TB) for more than a century, but only recently has consistent epidemiological evidence between tobacco and TB been established [1, 2]. Smokers are more likely to be infected with TB, progress to active disease and die from TB [3–5]. However, there are few worldwide studies regarding a dose–response relationship between the number of smoked cigarettes per day (CPD) and TB risk.

The aims of the present study were to evaluate the impact of smoking in TB risk and determine a threshold for tobacco consumption that increases the risk for active TB.

This cross-sectional study involved subjects recruited from primary healthcare outpatient units in northern Portugal, between August 2013 and September 2015. Cases corresponded to patients aged  $\geq 18$  years and diagnosed with active pulmonary TB. Controls were individuals aged  $\geq 18$  years with no suspicion or diagnosis of active TB including no history of TB in the participant's household within the previous 5 years. Pregnant and/or lactating women and individuals infected with HIV or other acquired immunosuppressive conditions were excluded from the study.

Clinical and socio-demographic data were collected. The clinical data included comorbidities such as diabetes, arterial hypertension, chronic kidney/liver/lung diseases, rheumatological diseases, solid/haematological malignancies, as well as other risk factors for TB infection, such as drug abuse, imprisonment, homelessness or residence in a community shelter. Other registered data included age, sex, area/type of residence, nationality, current occupation/employment, daily alcohol consumption, and smoking habits. Smoking status of the subjects was assessed according to their self-report, and the number of CPD was registered. This project was approved by Portugal's Northern Region Health Administration Ethics Committee. All participants provided written informed consent, and their anonymity was preserved during data analysis.

Separate analyses for men and women were performed as the observed patterns of tobacco consumption within each gender were quite different. The percentage of nonsmokers (no tobacco consumption) was 40% in men and 74% in women. As such, women were only grouped into either smokers (comprising current and ex-smokers) or nonsmokers. In men, smokers (encompassing current and ex-smokers) were grouped into two classes according to the criterion of maximisation of the area under the ROC curve. Mean  $\pm$  SD years of tobacco consumption were  $20 \pm 11.5$  for women and  $28.2 \pm 14.9$  for men. The crude effect of each evaluated variable on TB infection was investigated by simple logistic regression, except for those variables with very low numbers of TB infection. Those effects found to be statistically significant were later included in a multiple binary logistic regression model. The selection of the best model was based on the Akaike Information Criterion (AIC). The model discrimination ability was based on the area under the ROC curve. All statistical analyses were performed using the R language and software, version 3.3.2 ([www.r-project.org](http://www.r-project.org)). The level of significance was set at 0.05.

In all, 281 subjects were enrolled in this study (female: 50.2%). The mean  $\pm$  SD (range) age was  $51.9 \pm 17.3$  (19–87) years in men and  $51.4 \pm 17.1$  (19–85) years in women. The main results are summarised in table 1.

Upon splitting male smokers into two groups, the AUC maximum was attained at 17.5 CPD. A threshold at 20 CPD was thus set up as there were no observed values in between. Those with TB were significantly younger (53% with TB and  $\leq 45$  years *versus* 21% without TB and  $\leq 45$  years) and more likely to be



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**Excessive tobacco consumption in men (20 or more cigarettes per day) is a risk factor for tuberculosis**  
<http://ow.ly/AWdK30hdZOq>

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TABLE 1 Statistical description of the sample and results from the univariate and multivariate analysis

	Participants with TB	Participants without TB	p-value	Multivariate analysis	
				OR (95% CI)	p-value
<b>Males</b>					
Subjects n	74	66			
Age class ( $\leq 45$ years old)	39 (53%)	14 (21%)	<0.001	5.184 (2.361–12.091)	<0.001
Unemployment	22 (30%)	8 (12%)	0.014		
Diabetes mellitus	4 (5%)	34 (52%)	<0.001 <sup>#</sup>		
Alcohol consumption	9 (12%)	2 (3%)	0.063		
Arterial hypertension	7 (9%)	21 (32%)	0.002		
Chronic liver disease	5 (7%)	1 (2%)	0.162		
Tobacco consumption					
No	21 (28%)	35 (53%)	¶		
0–20 cigarettes per day	14 (19%)	13 (20%)	0.217	1.474 (0.534–4.074)	0.451
$\geq 20$ cigarettes per day	39 (53%)	18 (27%)	0.001	4.509 (1.971–10.859)	0.001
<b>Females</b>					
Subjects n	38	103			
Age class ( $\leq 45$ years old)	28 (74%)	32 (31%)	<0.001	5.895 (2.597–14.309)	<0.001
Unemployment	14 (37%)	17 (17%)	0.014	2.618 (1.046–6.579)	0.039
Diabetes mellitus	6 (16%)	45 (44%)	<0.004		
Alcohol consumption	0 (0%)	0 (0%)			
Arterial hypertension	4 (11%)	37 (36%)	0.002		
Chronic liver disease	1 (3%)	0 (0%)	+		
Smoking status					
Nonsmoker	23 (61%)	81 (79%)	¶		
Current/ex-smoker	15 (39%)	22 (21%)	0.003		

Data are presented as n (%), unless otherwise stated. In the univariate analysis, the p-value for the associated coefficient is presented. TB: tuberculosis. <sup>#</sup>: spurious value, as it results in an estimated OR of 19, the multivariate analysis did not consider this variable; ¶: reference class; +: the effect was not statistically evaluated as frequencies were very small.

unemployed (30% versus 12%). The crude analysis of cigarette consumption indicated that only men smoking at least 20 CPD had a significantly higher risk for TB than that of the nonsmokers. Individuals with arterial hypertension were less likely to have TB (9% versus 32%). For other variables, no significant differences were observed. The multiple logistic model evaluated all effects simultaneously and only the age class and the smoking pattern were found to have a statistically significant effect on the existence of TB-disease (AUC: 0.736). More precisely, being younger than 46 years increased the odds for TB by 5.2 times (95% CI: 2.361–12.091) and smoking 20 or more CPD increased the odds for TB by 4.5 times (95% CI: 1.971–10.859) compared to nonsmokers.

Those with TB were significantly younger (74% with TB and  $\leq 45$  years versus 31% without TB and  $\leq 45$  years) and more likely to be unemployed (37% versus 17%). Smokers were more likely to have TB (39% versus 21%) than nonsmokers. Those with arterial hypertension were less likely to have TB (11% versus 36%), and diabetes was positively associated with absence of TB. In the multiple logistic regression model, only the age group and the unemployment status were found to have a significant effect on TB (AUC: 0.744). In particular, being younger than 46 years increased the odds for TB by 5.9 times (95% CI: 2.597–14.309), while being unemployed increased the odds for TB by 2.6 times (95% CI: 1.046–6.579).

This study identified being younger than 46 years and smoking 20 or more CPD as the risk factors for TB in men, and being younger than 46 years and unemployed as the risk factors for TB in women.

According to prior reports, there is a significant association between both direct and second-hand smoke exposure and latent infection, active TB, more severe form of TB, lower rate of treatment success, and TB-related death [4–9]. Additionally, previous studies showed a statistically significant trend in the risk of TB with increasing number of CPD [10, 11]. However, to the best of our knowledge, there is only one previous work that has focused on the threshold number of cigarettes, indicating that smoking more than 20 CPD was an independent factor associated with TB [12]. We found a significantly higher risk of TB for men smoking 20 or more CPD in comparison with nonsmoking individuals, but no significant difference between the latter and those smoking up to 20 CPD. In women, a similar quantitative threshold was not possible as the sample consisted of a limited number of smoking women with TB. Moreover, the univariate effect of smoking status on TB was not significant when evaluated simultaneously with other risk factors.

Our results also indicated that young age increased the risk for TB, which is in agreement with worldwide data [13]. Unemployment, a well-known risk factor for TB, was also independently associated with TB in our study [14].

We did not find any prior reports consolidating our results regarding subjects with arterial hypertension and women with diabetes being less likely to have TB. However, this could be related with a reverse causality bias, if we consider that these individuals adopt a healthy lifestyle because they have a chronic disease.

For this study, we relied on self-reported tobacco consumption, which might be one limitation as it may not reflect the real smoking pattern of the subjects. In addition, although both passive and active exposures to cigarette smoke have been documented to be associated with TB, we only assessed active exposure in this study.

In conclusion, excessive tobacco consumption in men ( $\geq 20$  CPD) is a risk factor for TB. Other variables significantly associated with TB were unemployment and young age. Moreover, our analysis revealed a high prevalence of smoking among subjects with newly diagnosed TB. Thus, our results reinforce the need to integrate a smoking cessation strategy in all TB control programmes.

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