

## Letter to the Editor

### Smoker, Former Smoker and COVID-19: Nicotine Does Not Protect Against SARS-CoV-2\*

#### Fumador, exfumador y COVID-19: la nicotina no protege contra el SARS-CoV-2

To the Editor,

We would like to thank Moril et al.<sup>1</sup> for their interest in our paper and for prompting us to explore the topic further. The spike protein is responsible for facilitating the entry of SARS-CoV-2 into human cells and requires priming by protease TMPRSS2 to allow fusion of the viral and cellular membranes.<sup>2</sup> The receptor used by the spike protein is the angiotensin-converting enzyme 2 (ACE2),<sup>2</sup> which is expressed in different cell strains, as well as in the lung, where there is a gradient of ACE2 expression (higher expression in the upper respiratory tract [nasal epithelium] and lower in the

alveolar pneumocytes).<sup>2</sup> It has been suggested that a higher expression of ACE2 could contribute to increased SARS-CoV-2 viral infectivity.<sup>2</sup> As Moril et al. mention,<sup>1</sup> active smokers with chronic obstructive pulmonary disease have a higher level of expression of ACE2 than former smokers and former smokers have a higher level than never smokers,<sup>1,2</sup> while a decrease in ACE2 expression has been observed in the bronchial epithelial cells of former smokers compared with active smokers.<sup>1,2</sup> Not all authors have obtained the same results. Lee et al.<sup>3</sup> did not identify any differences in ACE2 expression based on age, sex, or smoking status, and suggest that smoking is not a protective factor, but rather a risk factor for Covid-19 disease progression. Voinsky et al.<sup>4</sup> did not find higher ACE2 and TMPRSS2 expression in smokers or never smokers, but they did observe higher expression of TMPRSS4 (that encodes a protease for cell entry similar to TMPRSS2) in smokers compared to never smokers, suggesting that they may be at increased risk for Covid-19 infection. Regarding the comment of Moril et al.<sup>1</sup> on

#### Former smokers

Studies	Estimate (95% C.I.)	Ev/Trt	Ev/Ctrl
Guan et al. 2020	4.146 (1.719, 9.997)	9/172	12/913
Zhang et al. 2020	1.951 (0.420, 9.066)	4/58	3/82
CDC Response team 2020	1.716 (1.079, 2.727)	33/457	45/1037
Chen et al. 2020	0.562 (0.107, 2.950)	2/113	5/161
Li et al. 2020	2.063 (1.131, 3.762)	33/265	18/279
<b>Overall (I<sup>2</sup>=24.63 %, P=0.257)</b>	<b>1.998 (1.321, 3.022)</b>	<b>81/1065</b>	<b>83/2472</b>

#### Smokers

Studies	Estimate (95% C.I.)	Ev/Trt	Ev/Ctrl
Guan et al. 2020	1.512 (0.967, 2.363)	29/172	108/913
Huang et al. 2020	0.270 (0.013, 5.617)	0/13	3/28
Zhang et al. 2020	7.301 (0.344, 154.960)	2/58	0/82
Zhou et al. 2020	2.228 (0.650, 7.633)	5/54	6/137
Wang et al. 2020	3.932 (1.296, 11.927)	7/25	9/100
CDC Response Team 2020	0.510 (0.192, 1.356)	5/457	22/1037
Wan et al. 2020	0.279 (0.034, 2.307)	1/40	8/95
Mo et al. 2020	1.679 (0.298, 9.449)	4/85	2/70
Chen et al. 2020	2.060 (0.637, 6.664)	7/113	5/161
Goyal et al. 2020	0.861 (0.323, 2.294)	6/130	14/263
Li et al. 2020	0.811 (0.427, 1.540)	18/265	23/279
<b>Overall (I<sup>2</sup>=38.18 %, P=0.095)</b>	<b>1.240 (0.812, 1.894)</b>	<b>84/1412</b>	<b>200/3165</b>

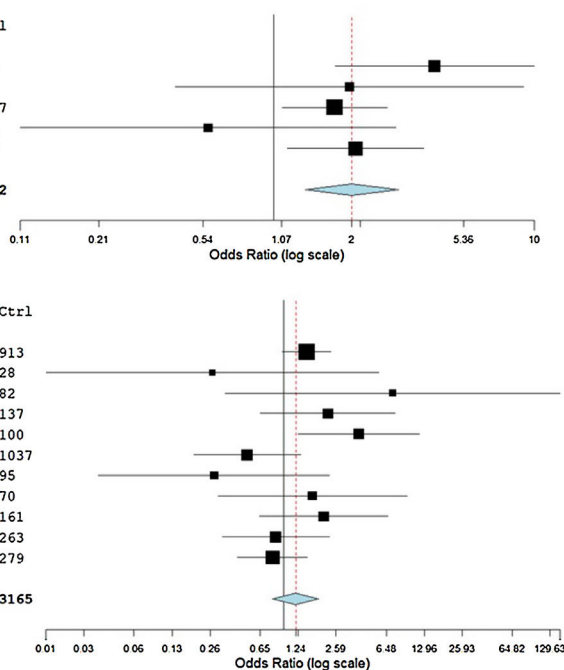


Fig. 1. Being a former smoker or an active smoker is a risk factor for worse Covid-19 progression.

\* Please cite this article as: Jiménez-Ruiz CA, López-Padilla D, Alonso-Arroyo A, Aleixandre-Benavent R, Solano-Reina S, de Granda-Orive JI. Fumador, exfumador y COVID-19: la nicotina no protege contra el SARS-CoV-2. Arch Bronconeumol. 2021. <https://doi.org/10.1016/j.arbres.2021.01.005>

the possibility of a better prognosis in smokers, Takagi, in Japan,<sup>5</sup> carried out a meta-regression that showed a positive association between the prevalence of smoking and Covid-19 infection independent of other co-variables, so the hypothesis that smokers have a better disease prognosis is not supported. In a new meta-analysis of our data,<sup>6</sup> we classified patients as smokers or former smokers (only 5 articles differentiated former smokers) (Fig. 1). Former smokers clearly showed similarly poor progression, while current smokers showed a clear tendency to worse progression but without statistical significance. The same results were obtained in the meta-analysis of Patanavanich et al.<sup>7</sup> (only 8 articles divided smokers into categories). Most of the studies included in the meta-analysis have significant limitations: they are mostly retrospective and have significant selection and data biases and lack a comparative group, making it difficult to establish causality. We reaffirm that smokers and former smokers have a worse Covid-19 progression, including higher mortality, and that nicotine cannot be considered a protective factor in any way.

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