

7. Tomchaney M, Contoli M, Mayo J, Baraldo S, Shuaizhi L, Cabel CR, et al. Paradoxical effects of cigarette smoke and COPD on SARS-CoV2 infection and disease. *bioRxiv*. 2020, <http://dx.doi.org/10.1101/2020.12.07.413252>, 12.07.413252.
8. Brake SJ, Barnsley K, Lu W, McAlinden KD, Eapen MS, Sohal SS. Smoking upregulates angiotensin-converting enzyme-2 receptor: a potential adhesion site for novel Coronavirus SARS-CoV-2 (Covid-19). *J Clin Med*. 2020;9:841, <http://dx.doi.org/10.3390/jcm9030841>.
9. <https://www.newstatesman.com/archive/2013/12/british-people-would-rather-go-down-fighting>.

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Tobacco and COVID-19: A position from Sociedade Portuguesa de Pneumologia. Authors' reply



We read with great interest the letter by Rossato and Di Vincenzo¹ commenting on our editorial "Tobacco and COVID-19: A position from Sociedade Portuguesa de Pneumologia" published in *Pulmonology* in December 2020.² We would like to thank the authors for the challenging discussion points and we acknowledge that, as in all fields of science, new data are continuously being collected and interpreted and we are still far from definitive conclusions about how smoking really impacts COVID-19.

The observations that report a low rate of smokers among COVID-19 patients are pertinent but have yet to be confirmed by good quality epidemiological studies designed to address this question. As we mentioned, a high number of studies does not report smoking status or does not distinguish never-smokers from missing data and this may pose considerable bias.² At the present time, we cannot rule out the hypothesis that smoking may not constitute a strong risk factor for COVID-19, but we have to further specify what questions we are posing: what is the difference in risk between present smokers and having a past history? Are smokers more prone to contract SARS-CoV-2 infection in general? We do not have enough information concerning asymptomatic infection and smoking, and we know there may be a bias toward higher testing rates in smokers,³ due to higher rates of respiratory symptoms. An interesting study in *Nature*⁴ shows that there are difficulties in correctly adjusting for other covariates – depending on the covariates included, a smoking history could either be associated with a higher risk of COVID-19 (age and sex adjusted only) or lower risk (fully adjusted model). After adjusting only for demographic factors (age, sex, deprivation and ethnicity), the authors found a non-significant positive hazard ratio for current smoking (HR 1.07 (0.98–1.18)), excluding any protective effect of nicotine and suggesting that any increased risk with current smoking is likely to be small.

Rossato and Di Vincenzo also quote the new paper by Tomchaney et al.,⁵ reporting conflicting new results that show decreased expression of ACE2 receptors in both bronchial and alveolar epithelial cells exposed to cigarette smoke.

These are puzzling data that still wait peer-review and publication. Animal studies are undoubtedly important to open new pathophysiologic hypothesis; however, we still face uncertainties as to the real role of ACE-2 receptor modulation and the risk of infection. One of the problems concerns tobacco smoke, a mixture of thousands of chemicals interacting together, and the presumptive role of nicotine. The studies by Russo et al.⁶ have thrown some light on how isolated nicotine may facilitate SARS-CoV-2 infection: nicotine, even at low concentrations, increases ACE-2 levels in bronchial cells. Besides, they showed that ACE-2 increase is specifically mediated by $\alpha 7$ -nAChR, suggesting that smoking may promote cellular uptake mechanisms of SARS-CoV-2 through $\alpha 7$ -nAChR signaling. The presence of this receptor in neuronal tissues also raises questions about the impact of smoking in COVID-19 pathophysiology in several organs, including the brain.

In the absence of well-designed studies, with large populations, any hypothesis on the effect of smoking or nicotine in the risk of COVID-19 remains unproven. More than five decades of research in vast population-based studies were needed to establish the causative effect of tobacco in several deadly diseases. Our minds should be open to change, but in the present state of knowledge, we stand with the WHO and adopt a cautious recommendation against any putative protective effect of smoking.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Rossato M, Di Vincenzo A. Cigarette smoking and COVID-19. *Pulmonology*. 2021, <http://dx.doi.org/10.1016/j.pulmoe.2020.12.013>.
2. Matos CP, Boléo-Tomé JP, Rosa P, Morais A. Tobacco and COVID-19: a position from Sociedade Portuguesa de Pneumologia. *Pulmonology*. 2021;27(2):91–3, <http://dx.doi.org/10.1016/j.pulmoe.2020.11.002>.
3. Simons D, Shahab L, Brown J, Perski O. The association of smoking status with SARS-CoV-2 infection, hospitalisa-

- tion and mortality from COVID-19: a living rapid evidence review with Bayesian meta-analyses (version 8). Qeios; 2020. <http://dx.doi.org/10.32388/UJR2AW.11>.
4. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature*. 2020;584:430–6. <http://dx.doi.org/10.1038/s41586-020-2521-4>.
 5. Tomchaney M, Contoli M, Mayo J, Baraldo S, Shuaizhi L, Cabel CR, et al. Paradoxical effects of cigarette smoke and COPD on SARS-CoV2 infection and disease. *bioRxiv*. 2020;(December), <http://dx.doi.org/10.1101/2020.12.07.413252>, 2020.12.07.413252 (preprint).
 6. Russo P, Bonassi S, Giacconi R, Malavolta M, Tomino C, Maggi F. COVID-19 and smoking: is nicotine the hidden link? *Eur Respir J*. 2020;55(6):2001116. <http://dx.doi.org/10.1183/13993003.01116-2020> [Published 4 June 2020].

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For a patient with severe asthma, every day may be his last *World Asthma Day*



KEYWORDS

Asthma;
Biologics;
Control;
Costs;
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World Asthma Day

Dear Editor,

We read carefully the interesting article of Arrobas et al “Cost-effectiveness of omalizumab in real world uncontrolled allergic asthma patients” recently published on *Pulmonology*.¹

We congratulate the authors for considering all important aspects for patients with severe asthma. They included real world patients with asthma that do not always match with those included in randomized placebo-controlled trials;¹ recognized that a significant percentage of patients have uncontrolled asthma, a rate that is particularly higher in severe asthmatic patients;² uncontrolled asthma, especially uncontrolled severe asthma, was associated with increased direct and indirect costs,³ as previously found in our country including a representative sample of patients;² data that come from well-designed cost-effectiveness study like this is generally not considered in national healthcare plans for asthma; the specialist-based indication for biologic drugs such as omalizumab in severe allergic persistent asthma, as in the current study, allowed the reduction of exacerbation

rates and increased patients’ quality of life, at a societal acceptable cost.^{1,4}

Nowadays, it is unacceptable to treat severe asthmatic patients with oral corticosteroids (OCS) on a daily basis or even during their almost permanent exacerbations.^{1,4} Therefore, we need innovative drugs. The low price of OCS opposes the very high expenses in morbidity and mortality.⁴

We acknowledge the authors because this study will probably give important and relevant support to our national health authorities’ decisions in severe asthma care, including our national investments. Similar to other patients with immune-related diseases, severe asthmatics from all ages have the right of equity. People living with severe asthma from all the regions must have access to treatments that, despite not being able to modify the natural history of the disease, can definitely modify their lives. Access to these treatments should be constant, even in a particularly difficult times related with the current Coronavirus Disease 2019 (COVID-19) outbreak.⁵

Patients with severe asthma are included in the high risk group for COVID-19 worse prognosis; it is time to maintain asthma under control. All treatments must be used, from inhaled corticosteroids to biologicals, as they were before the outbreak. No risk of increased viral infection susceptibility has been reported to date in previous placebo controlled trials and real world studies with omalizumab, mepolizumab, benralizumab, reslizumab and dupilumab in asthmatic patients. Regarding omalizumab, there is a possible anti-infectious effect. Thus, physicians must maintain biological treatments during the current pandemic.⁵

The World Asthma Day on May 5th 2020 is the first one in the COVID-19 era. Patients with severe asthma are once again concerned with COVID-19 morbidity and mortality, along with patients with other well-known chronic diseases, in particular metabolic, cardiovascular and chronic obstructive pulmonary disease.